INTERNATIONAL RECORD OF MEDICINE

&

GENERAL PRACTICE CLINICS

VOLUME 169 NO. 10 | OCTOBER 1956

ORIGINALLY PUBLISHED AS AMERICAN MEDICAL INTELLIGENCER, FOUNDED PHILADELPHIA, 1837

Topical and Systemic Chemotherapy of Suppurative Lung Disease — Edwin J. Grace

The Use of Tetracycline-Vitamin Combination in Acute Infections — H. Marvin Daskal

The Use of a Sustained-Release *d*-Amphetamine-Amobarbital Preparation in the Treatment of Obesity — Richard P. Shapiro and Kenneth I. Michaile

The Action of Salicylate as Related to Pituitary-Adrenal Function — Charles H. Eades, Jr., and J. Stanton King, Jr.

On the Psychology of Symbolism in Oriental Rugs — Felix Martí-Ibáñez

Editorial Survey: Genesis of Cancer

International Clinical Newsletter

Advanced Reports from Current Medical Meetings

A JOURNAL OF MD PUBLICATIONS, INC.

MD INTERNATIONAL SYMPOSIA MONOGRAPH No. 3

Psychiatry *and* Religion

Thirteen scientific authorities and ministers of different religions explore the conflicts of the human psyche and open up new vistas for meaningful cooperation between the psychiatrist and churchman. An absorbing discussion of interest to the psychologist, sociologist, anthropologist, psychiatrist, theologian, religious historian, the clergy, and the intelligent layman. A most unusual and attractively bound volume. 68 pp. **Price: $3.00.**

C O N T E N T S

SYMPOSIUM ON PSYCHIATRY AND RELIGION
An Introduction by Werner Wolff, Ph.D., Professor of Psychology, Bard College, Annandale-on-Hudson, N. Y.

THE PSYCHE AND THE SYMBOLS OF RELIGION
by M. Esther Harding, M.D., M.R.C.P., New York City.

PSYCHOANALYSIS AND RELIGION, AN HISTORICAL VIEW OF FREUD
by Fred H. Blum, Dept. of General Studies, Social Science Program, University of Minnesota, Minneapolis, Minn.

A CURRENT PSYCHOANALYTIC CONCEPT OF GOD
by Josephine H. Ross, Ph.D., New York City.

ANTHROPOLOGIC VIEW OF A PRIMITIVE RELIGION
by Gladys A. Reichard, Professor of Anthropology, Barnard College, Columbia University, New York City.

THE SOCIOLOGIC DEFINITION OF RELIGION
by Joseph Maier, Ph.D., M.A., Newark College of Arts and Sciences, Rutgers University, New Brunswick, N. J.

TOWARDS AN OPERATIONAL DEFINITION OF RELIGION
by Rabbi Samuel Glasner, Ed.D., Director, Dept. of Reform Jewish Education, Board of Jewish Education, Baltimore, Md.

RELIGION AND PSYCHOTHERAPY: PRACTICAL ASPECTS
by Lawson G. Lowrey, M.D., A.M., Asst. Clinical Professor, College of Physicians and Surgeons, Columbia University; Associate in Psychiatry, Vanderbilt Clinic, New York City.

VALUE SYSTEMS IN THE PSYCHOTHERAPEUTIC PROCESS
by Warner L. Lowe, Ph.D., Asst. Director, Alfred Adler Mental Hygiene Clinic, New York City.

PERSONALITY NEEDS, RELIGION, AND PSYCHOTHERAPY
by Alexander A. Schneiders, Ph.D., Professor of Psychology and Director of Psychological Services, Fordham University, New York City.

PSYCHOTHERAPY AND THE MINISTRY
by Abraham N. Franzblau, M.D., Ph.D., Professor of Pastoral Psychiatry and Dean of New York Schools, Hebrew Union College, Jewish Institute of Religion; Asst. Attending Psychiatrist, Mount Sinai Hospital, New York City.

THE NEED TO BELIEVE
by Mortimer Ostow, M.D., New York City.

SPECIAL EDITORIAL:
On Christmas and Neuroses
by Félix Martí-Ibáñez, M.D.

WRITE TO: MD PUBLICATIONS, INC., 30 EAST 60TH STREET, NEW YORK 22, N. Y.

INTERNATIONAL RECORD OF MEDICINE

A JOURNAL OF ADVANCED EXPERIMENTAL AND CLINICAL REPORTS

&

GENERAL PRACTICE CLINICS

ORIGINALLY PUBLISHED AS AMERICAN MEDICAL INTELLIGENCER, FOUNDED PHILADELPHIA, 1837

FELIX MARTI-IBAÑEZ, M.D., Editor

VOL. 169 NO. 10 *WHOLE NUMBER 2884* *OCTOBER 1956*

The *International Record of Medicine and General Practice Clinics* is published monthly by MD Publications, Inc. (30 E. 60th Street, New York, N. Y., Félix Martí-Ibáñez, M.D., President). ©Copyright 1956 by MD Publications, Inc. Entered as second class matter at the Post Office, Washington, D. C., under the Act of March 3, 1879. Matter appearing in *International Record of Medicine and General Practice Clinics* is covered by copyright. The reproduction of articles (or parts of articles) appearing in *International Record of Medicine and General Practice Clinics* is not permitted. Permission must be received in writing from the editor for reprinting material in whole or in part. Subscription Rate: $11.00 for one year, $28.00 for three years.

INTERNATIONAL RECORD OF MEDICINE AND GENERAL PRACTICE CLINICS

INSTRUCTIONS TO CONTRIBUTORS

All manuscripts submitted for publication in INTERNATIONAL RECORD OF MEDICINE should be sent to Doctor Félix Martí-Ibáñez, MD Publications, 30 East 60th St., New York 22, N. Y. Manuscripts should not include data published previously and it is understood that any manuscript submitted is not being submitted elsewhere.

Manuscripts—All manuscripts should be typewritten, double spaced, and on only one side of paper 8½ by 11 inches. They should be mailed in a flat package. *The original, one carbon copy, and an abstract (approximately 250–300 words) of the article are required.* Original drawings or tracings should not be sent. Glossy photographs, no larger than the manuscript paper, of all illustrations should accompany the copies of the manuscript. Prints should be sufficiently clear to permit the making of engraver's cuts without retouching and to allow reduction to approximately one-third size.

Tables, figures, charts, etc., must be typewritten on separate sheets and should be placed in proper sequence in the manuscript. Footnotes should not be included in the text pages. All references are to be numbered consecutively and typed on a separate sheet. Numerals are used for figures for all definite weights, measurements, percentages, and degrees of temperatures. All indefinite and approximate periods of time and other numerals which are used in a general manner should be spelled out. Standard abbreviations should be used whenever weights and measurements are given in the metric system. The forms to be used are: Gm., ml., Kg., mg., μg., mm., and l. Per cent should be written out in the text.

Footnotes and Bibliographies should conform to the style of the Quarterly Cumulative Index Medicus published by the American Medical Association. This requires, in the order given, last name of author, initials, title of article in the language in which it was written, name of journal with accepted abbreviation, volume number, page number, and year.

Illustrations.—A reasonable number of half-tone illustrations will be reproduced free of cost to the author but special arrangements must be made with the editor for color plates, elaborate tables, or extra illustrations. Pen drawings and charts should be drawn and lettered only in India ink or black typewritter ribbon (when the typewriter is used). Only good photographic prints or drawings should be supplied for half-tone work. All photographs submitted should be numbered and bear on the back author's name, address, and title of article. Top of picture should be indicated.

Reprints.—Authors will be sent an estimate of the cost of reprints with galley proofs. Reprints may be ordered anytime after manuscript has been set in type but not later than 30 days after the journal has been published.

Business Communications.—All communications in regard to advertising, subscription, change of address, etc., should be addressed to M D Publications, Inc., 30 East 60th Street, New York 22, N. Y. The publisher should be advised of a change in the subscriber's address about 15 days before the date of the issue of the journal with both new and old addresses given.

Subscription Rates.—In the United States and other countries in the United States postal zone—$11.00; single copies, $1.20. In Canada and other foreign countries—$12.00; single copies, $1.40. Remittance for subscriptions should be made by check, draft, post office or express money order, or registered letter payable to M D Publications, Inc.

d-spectrum rapy as good as it tastes!
TETRABON*
BRAND OF TETRACYCLINE
HOMOGENIZED MIXTURE
125 mg. tetracycline per 5 cc. teaspoonful. Bottles of 2 fl. oz. and 1 pint, packaged ready to use (no reconstitution required).
READILY ACCEPTED delightfully different fruit flavor . . .
RAPIDLY ABSORBED fine particle dispersion—therapeutic blood levels within one hour . . .
QUICKLY EFFECTIVE well-tolerated tetracycline for prompt control of a wide range of infections.
*Trademark
PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, N.Y.
Pfizer

MD INTERNATIONAL SYMPOSIA MONOGRAPH No. 2

MEDICAL WRITING

Good writing is just as essential in the medical profession as in any other field.

In this symposium, a panel of distinguished medical writers describe the how and why of writing clear and cogent medical articles and books.

Invaluable for the physician interested in the practical principles of medical writing, as well as the enrichment of his own culture in the medical humanities.

A very unusual and attractive book gift for a fellow physician.

72 pp. **Price: $3.00.**

contents

THOUGHTS ON THE PHYSICIAN'S WRITING AND READING
by Henry Sigerist, M.D., Pura, Ticino, Switzerland.

HOW NOT TO WRITE A MEDICAL PAPER
by Hans Selye, M.D., Professor and Director, Institut de Médecine et de Chirurgie Expérimentales, Université de Montréal, Canada.

AN EDITOR'S PREJUDICES
by Hugh Clegg, M.D., Editor, British Medical Journal, *London, England.*

MEDICAL WRITING
by Walter C. Alvarez, M.D., former Professor of Medicine, University of Minnesota; Editor, Modern Medicine, *Chicago, Ill.*

BOOKS IN THE PHYSICIAN'S LIFE
by Félix Martí-Ibáñez, M.D., Editor-in-Chief, International Record of Medicine & General Practice Clinics, *New York City.*

WRITE TO: MD PUBLICATIONS, INC., 30 EAST 60TH STREET, NEW YORK 22, N. Y.

EDITORIAL BOARD

FELIX MARTI-IBAÑEZ, M.D., Editor

NATIONAL EDITORIAL BOARD

FRED L. ADAIR, M.D., *University of Chicago*

HARRY L. ARNOLD, JR., M.D., *Editor, Hawaii Medical Journal, Honolulu, Hawaii*

W. WAYNE BABCOCK, M.D., *Temple University*

HOWARD C. BALLENGER, M.D., *Northwestern University*

CONRAD BERENS, M.D., *The Ophthalmological Foundation*

ALEXANDER W. BLAIN, M.D., *Wayne University*

ALFRED BLALOCK, M.D., *Johns Hopkins University*

W. F. BRAASCH, M.D., *Mayo Clinic*

ROBERT H. BROH-KAHN, M.D., *New York, N. Y.*

MORTON S. BRYER, M.D., *The Mount Sinai Hospital*

LEROY A. CALKINS, M.D., *University of Kansas*

NORTON CANFIELD, M.D., *New Haven, Conn.*

BAYARD CARTER, M.D., *Duke University*

RUSSELL L. CECIL, M.D., *Cornell University*

F. CO TUI, M.D., *Creedmoor Institute*

FREDERICK A. COLLER, M.D., *University of Michigan*

WILLARD R. COOKE, M.D., *University of Texas*

WALTER T. DANNREUTHER, M.D., *New York University*

CLYDE L. DEMING, M.D., *Yale University School of Medicine*

R. S. DINSMORE, M.D., *Cleveland Clinic*

HENRY DOLGER, M.D., *New York, N. Y.*

I. E. DRABKIN, PH.D., *The College of the City of New York*

DANIEL C. ELKIN, M.D., *Emory University*

LUDWIG A. EMGE, M.D., *Stanford University*

HAROLD K. FABER, M.D., *Stanford University Hospital*

HARRY A. FELDMAN, M.D., *State University of New York*

JOSEPH H. FOBES, M.D., *New York Medical College*

A. STONE FREEDBERG, M.D., *Harvard Medical School, Boston, Mass.*

WILLIS D. GATCH, M.D., *University of Indiana*

LOUIS J. GELBER, M.D., *Rockville Center, L. I., N. Y.*

DAVID GROB, M.D., *Johns Hopkins Medical School*

BERNARD J. HANLEY, M.D., *University of Southern California*

FRENCH K. HANSEL, M.D., *Washington University*

CLYDE A. HEATLY, M.D., *University of Rochester*

HENRY F. HELMHOLTZ, M.D., *Mayo Clinic*

FRANK HINMAN, M.D., *University of California*

CLARENCE B. INGRAHAM, M.D., *University of Colorado*

J. BAY JACOBS, M.D., *Georgetown University*

ROBERT W. KEETON, M.D., *University of Illinois*

HARRY H. KERR, M.D., *George Washington University*

WILLIAM J. KERR, M.D., *Blue Lake, California*

I. NEWTON KUGELMASS, M.D., *New York, N. Y.*

THEODORE LIDZ, M.D., *Yale University School of Medicine*

DEAN M. LIERLE, M.D., *University of Iowa*

IRVINE MCQUARRIE, M.D., *University of Minnesota*

RALPH H. MAJOR, M.D., *University of Kansas*

ALTON OCHSNER, M.D., *Tulane University*

HENRY BOYLAN ORTON, M.D., *Newark, N. J.*

WINFRED OVERHOLSER, M.D., *George Washington University*

JAMES E. PAULLIN, M.D., *Emory University*

FRANKLIN L. PAYNE, M.D., *University of Pennsylvania*

E. D. PLASS, M.D., *University of Iowa*

TRACY J. PUTNAM, *Beverly Hills, California*

B. O. RAULSTON, M.D., *University of Southern California*

LYMAN G. RICHARDS, M.D., *Massachusetts Institute of Technology*

LEONARD G. ROWNTREE, M.D., *Miami, Fla.*

RAYMOND R. SACKLER, M.D., *New York, N.Y.*

MILTON S. SACKS, M.D., *University of Maryland School of Medicine*

MORRIS SCHAEFFER, M.D., *Director, Communicable Disease Center, Montgomery, Ala.*

LEWIS C. SCHEFFEY, M.D., *Jefferson Medical College*

SIDNEY SCHERLIS, M.D., *University of Maryland School of Medicine*

EDWARD A. SCHUMANN, M.D., *Phila., Pa.*

CYRUS C. STURGIS, M.D., *University of Michigan*

HERBERT THOMS, M.D., *Yale University*

DONALD V. TRUEBLOOD, M.D., *Seattle, Wash.*

JAMES J. WARING, M.D., *University of Colorado*

KARL M. WILSON, M.D., *University of Rochester*

FRED W. WITTICH, M.D., *Minneapolis, Minn.*

FLETCHER D. WOODWARD, M.D., *Charlottesville, Va.*

INTERNATIONAL EDITORIAL BOARD

ROMA AMYOT, M.D., *Editor-in-Chief, L'Union Medicale du Canada*

GASTON BACHELARD, M.D., *Directeur de l'Institut d'Histoire des Sciences, La Sorbonne, Paris, France*

GEOFFRY H. BATEMAN, *London, England*

F. CASADESUS, *Barcelona, Spain*

PAUL DIEPGEN, M.D., *Director of Medizinhistorischen Institutes der Johannes Gutenberg Univ., Mainz, Germany*

PEDRO LAIN ENTRALGO, M.D., *Profesor de Historia de la Medicina, Madrid, Spain*

PROF. A. GIGON, *Schweizerische Akademie der Medizinischen, Wissenschaften, Basel, Switzerland*

EDV. GOTFREDSEN, M.D., *Director of the Universitetets Medicinsk-Historiske Museum, Copenhagen, Denmark*

DOUGLAS GUTHRIE, M.D., *Professor of the History of Medicine, University of Edinburgh, Edinburgh, Scotland*

WILLY HARTNER, M.D., *Johann Wolfgang Goethe Universität, Frankfurt a. M., Germany*

E. HINTZCHE, M.D., *Anatomisches Institut Bern, Switzerland*

BJORN IBSEN, M.D., *Kobenhavns Hospitalvaesen, Communehospitalet, Kobenhaven, Denmark*

JUAN B. LASTRES, M.D., *Profesor de Historia de la Medicina, Universidad de San Marcos, Lima, Peru*

TRULS LEEGAARD, M.D., *Oslo, Norway*

W. J. MCNALLY, M.D., *Quebec, Canada*

ADOLF MEYER-ABICH, M.D., *Hamburg-Blankenese, Elbchaussee 460, Germany*

ANDRE MOULONGUET, M.D., *Paris, France*

JO ONO, M.D., *Tokyo, Japan*

PROF. RODOLFO PÉREZ DE LOS REYES, *Universidad de La Habana, Cuba*

AUGUSTO PI-SUÑER, M.D., *Instituto de Medicina Experimental, Caracas, Venezuela*

M. A. PRECECHTEL, *Praha, Czechoslovakia*

ANTONIO DA COSTA QUINTA, *Lisbon, Portugal*

ILSE ROSENTHAL-SCHNEIDER, Ph.D., *The University of Sydney, Sydney, Australia*

ANIBAL RUIZ MORENO, M.D., *Profesor de Historia de la Medicina, Buenos Aires, Argentina*

KENNETH F. RUSSELL, M.S., F.R.A.C.S., *Associate Professor of Anatomy, The University of Melbourne, Melbourne, Australia*

TH. H. SCHLICHTING, M.D., *Amsterdam, Holland*

HANS SELYE, M.D., *Université de Montréal, Montreal, Canada*

PROF. IVOLINO DA VASCONCELLOS, *President, Sociedad Brasileña de de Historia da Medicina, Rio de Janeiro, Brazil*

a new concept of medicine:

Stress

FIFTH ANNUAL REPORT 1955-1956

editors

HANS SELYE, M. D., Ph. D. (Prague), D. Sc. (McGill), F. R. S. (Canada), F. I. C. S. Professor and Director, Institut de Médicine et de Chirurgie expérimentales, University of Montreal.

GUNNAR HEUSER, M. D. (Cologne), Research Assistant and Librarian of the Institut de Médicine et de Chirurgie expérimentales, University of Montreal.

FOR THE CLINICIAN—new clinical perspectives in the treatment of diseases of adaptation.

FOR THE RESEARCH WORKER—a wealth of experimental data in biopathology and endocrinology.

FOR THE TEACHER—the most complete survey of the stress concept in modern medicine. In addition to Dr. Hans Selye's own original research work, special articles include:

special new articles

- PRIMARY ALDOSTERONISM, A NEW CLINICAL ENTITY by Jerome W. Conn and Lawrence H. Louis, University of Michigan.
- HORMONAL INFLUENCES ON INFLAMMATION AND DETOXIFICATION by T. F. Dougherty and R. D. Higginbotham, University of Utah.
- STRESS AND CATHECOL HORMONES by U. S. von Euler, Pysiologiska Institutionen, Stockholm, Sweden.
- ADRENAL INFLUENCES UPON THE STOMACH AND THE GASTRIC RESPONSE TO STRESS by S. J. Gray, G. Ramsey, R. Villareal and L. J. Krakauer, Peter Bent Brigham Hospital and Harvard Medical School.
- THE ROLE OF THE ADRENAL CORTEX IN THE ETIOLOGY OF DISEASE by D. J. Ingle, University of Chicago.
- ADRENOCORTICAL SECRETION AND FACTORS AFFECTING THAT SECRETION by D. H. Nelson, University of Utah.
- NEUROSECRETION by Ernst Scharrer, Albert Einstein College of Medicine, New York.
- SOME OBSERVATIONS ON PSYCHIATRIC STRESS IN INFANCY by R. A. Spitz, New York Psychoanalytic Institute.
- CORTISONE IN RELATION TO LYMPHOID TISSUE AND IMMUNITY by Herbert C. Stoerk, Merck Institute for Therapeutic Research.

A handsome, richly bound, fully illustrated volume of more than 800 pages, with a durable hard cover, published February, 1956, at the price of $20.00.

MD *PUBLICATIONS, INC., 30 EAST 60th STREET, NEW YORK 22, N.Y.*

health and travel

Complete proceedings of the First Symposium on Health and Travel, held in June of 1955. Travel for the young, the old, the sick; by car, air, train, boat, and space ship; in the continental U. S., Europe, Latin America, Asia; in tropical and subtropical climes. All these problems are covered in their physiologic and psychologic aspects by top specialists in their field. The monograph includes detailed information on prophylaxis and treatment, as well as historical and entertaining general data. This attractive hard-cover book is a classic reference book for your library, as well as an attractive and much appreciated gift for a fellow physician. 72 pp. **Price: $3.00.**

contents

THE PHYSICIAN AS TRAVELER
by Félix Martí-Ibáñez, M.D., Editor-in-Chief, INTERNATIONAL RECORD OF MEDICINE & GENERAL PRACTICE CLINICS.

WHEN CHILDREN TRAVEL
by I. Newton Kugelmass, M.D., Consultant, Dept. of Health & Hospitals, New York City.

WHEN PEOPLE WHO ARE NOT YOUNG TRAVEL
by William T. Foley, M.D., Assistant Professor of Clinical Medicine & Chief of the Vascular Clinics, New York Hospital, New York City.

INFECTIONS AND TRAVEL
by Elmer H. Loughlin, M.D., Associate Clinical Professor of Medicine, New York Medical College, Flower & Fifth Avenue Hospital, New York City.

WHEN SICK PEOPLE TRAVEL
by Walter C. Alvarez, M.D., Editor-in-Chief, MODERN MEDICINE

TRAVEL AND MOTION SICKNESS
by Herman I. Chinn, Ph.D., Chief, Dept. of Pharmacology-Biochemistry, USAF School of Aviation, Randolph Field, Texas.

STRESS AND TRAVEL
by Gaétan Jasmin, M.D., Institute of Experimental Medicine, Montreal, Canada.

SEA TRAVEL AND HEALTH
by William L. Wheeler, Jr., M.D., Medical Director, W. R. Grace & Company, New York City.

GEOGRAPHY, TRAVEL AND DISEASE
by Jacques, M. May Head, Dept. of Medical Geography, American Geographical Society, New York City.

MEDICAL PROBLEMS OF SPACE FLIGHT
by Hubertus Strughold, M.D., Chief, Dept. of Space Medicine, USAF School of Aviation Medicine, Randolph Field, Texas

PHYSIOLOGIC DAY-NIGHT CYCLE AFTER LONG DISTANCE FLIGHTS
by Hubertus Strughold, M.D., Ph.D., Chief, Dept. of Space Medicine, USAF School of Aviation Medicine, Randolph Field, Texas.

NUTRITION AND FLIGHT
by Col. Miriam E. Perry, Chief, Women's Medical Specialist Corps, USAF, Office of Surgeon General, Washington, D. C.

NEW PERSPECTIVES OF HEALTH AND TRAVEL. A SUMMATION OF THE SYMPOSIUM
by Félix Martí-Ibáñez, M.D., Editor-in-Chief of the INTERNATIONAL RECORD OF MEDICINE & GENERAL PRACTICE CLINICS.

WRITE TO: MD PUBLICATIONS, INC., 30 EAST 60TH STREET, NEW YORK 22, N. Y.

INTERNATIONAL RECORD OF MEDICINE

& GENERAL PRACTICE CLINICS

VOL. 169 NO. 10 *WHOLE NUMBER 2884* *OCTOBER 1956*

Edwin J. Grace	Topical and Systemic Chemotherapy of Suppurative Lung Disease	631
H. Marvin Daskal	The Use of Tetracycline-Vitamin Combination in Acute Infections	636
Richard P. Shapiro and Kenneth I. Michaile	The Use of a Sustained-Release *d*-Amphetamine-Amobarbital Preparation in the Treatment of Obesity	638
Charles H. Eades, Jr., and J. Stanton King, Jr.	The Action of Salicylate as Related to Pituitary-Adrenal Function	642
Felix Martí-Ibañez	On the Psychology of Symbolism in Oriental Rugs	651
	International Clinical Newsletter	opp. p. 662
	Editorial Survey: Genesis of Cancer	663
	GENERAL PRACTICE CLINICS *Advanced Reports from Current Medical Meetings*	
Martin W. Meyer	Intensive Recreational Activity in Treatment of Schizophrenic Patients	665
Raymond W. Brust	Clinical Aspects of Collagen Diseases	666
Robert F. Pitts	Mode of Action of the Mercurial Diuretics	667
Maxwell Finland	New Antibiotic Concepts	668
Kenneth C. Hutchin	Sigmoidoscopy in General Practice	670
D. W. Woolley	A Biochemical Approach to the Chemotherapy of Cancer	671
Julian B. Herrmann	Hormonal Therapy of Breast Carcinoma	672
Victor F. Marshall	Pyuria in Infancy	673
Thomas V. Santulli	Intestinal Obstruction in the Newborn	675
Paul McGuff	Endometriosis as a Cause of Intestinal Obstruction	675
Jacob Fine	Effect of Vascular Collapse on Infection by Microorganisms	676
Paul D. White	Coronary Artery Disease	677

In the November issue:

A Symposium on Medicine and Writing will be published in the November issue of the International Record of Medicine & General Practice Clinics. Articles to be included are: "Plain Talk and Clear Writing," by Morris Fishbein; "The Principles of Bibliographic Citation: an Informal Discourse Addressed to Writers of Scientific Papers," by John F. Fulton; "On Writing a History of Medicine," by Douglas Guthrie; "The Art of Communication," by Joseph Garland; "The Editing of a Modern Medical Textbook," by Russell L. Cecil; and "Minerva and Aesculapius: The Physician as Writer," by Félix Martí-Ibáñez.

in surgery–

THORAZINE*

- **alleviates anxiety, tension and fear**
- **stops vomiting, retching and hiccups**
- **reduces the need for narcotics and sedatives**
- **lessens the amount of anesthetic required**
- **controls emergence excitement**

provides a smoother course for your surgical patient

'Thorazine' is available in ampuls, tablets and syrup, as the hydrochloride; and in suppositories, as the base.

'Thorazine' should be administered discriminately; and, before prescribing, the physician should be fully conversant with the available literature.

Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.

INTERNATIONAL RECORD OF MEDICINE

VOL. 169 NO. 10 WHOLE NUMBER 2884 OCTOBER 1956

Topical and Systemic Chemotherapy of Suppurative Lung Disease

Edwin J. Grace, M.D.

BROOKLYN, N. Y.

It is now possible to judge the effectiveness of multiple chemotherapy in pulmonary tuberculosis with the confidence of nearly a decade of clinical experience. It is clear that in streptomycin, isonicotinic acid hydrazide (isoniazid), and *p*-aminosalicylic acid (PAS), we have powerful antitubercular agents when they are used in combination;[1–6] it is equally clear that their success in clinical use will be limited by the methods employed in administering them topically with detergent solvents.[7] The speed with which resistance was observed to develop in step pattern to streptomycin, and later to isoniazid, when given alone threatened to destroy their therapeutic value;[8] the discovery that a combination of these effective drugs administered together could practically eliminate the development of resistance has led to the general abandonment of the use of any of them alone. The practice of combining several effective agents to prevent resistance is now entirely justified clinically as well as empirically. Resistance of *Mycobacterium tuberculosis* to a chemical agent occurs by genetic mutation. The frequency of mutation resistant toward two agents is the product of its frequency toward each agent alone; since the latter frequencies are small, their product may be infinitesimal.

This genetic principle as it applies to microbial populations has been well established by many workers in the last decade, and its implications for chemotherapy generally are now being recognized.[9] Finland,[10] in a recent discussion of antibiotic resistance, reports that combinations of agents delay or prevent the development of resistant strains of *Escherichia coli* and staphylococci, although he adds that studies on combinations have been done chiefly to investigate their additive or synergistic properties.

Regardless of the reason for the scarcity of clinical studies on this question, it is mainly in tuberculosis therapy that the idea of combinations has been employed primarily for the purpose of controlling resistance. This report will attempt to show that the principle involved here is not only valid in tuberculosis but may be extended as well to other suppurative disorders of the lung.

With regard to antitubercular agents, combinations of effective drugs appear to be generally additive but are probably not significantly synergistic, as judged by clinical findings such as roentgenographic clearing and sputum reversal. The question of synergism in tuberculosis therapy is particularly difficult to resolve because of the lack of clear-cut criteria of improvement; thus the simultaneous use of effective agents would seem to be justified solely by their effectiveness in preventing resistance.

It has not been so widely recognized as a principle of chemotherapy in pulmonary tuberculosis that besides systemic administration of combinations of agents, topical therapy with detergent solvents is practical, requires little special equipment, and in combination with simultaneous systemic therapy can be much more effective than systemic therapy alone.

Lesions with scant vascular supply may often receive subliminal concentrations of systemically administered agents; such lesions may progress by excavation and may serve as foci of new infection. It is rational to introduce adequate concentrations of effective agents by the bronchial route as well as by the vascular route in an attempt to reach all possible areas of involvement.

An aerosol inhalation apparatus, described elsewhere in detail,[11] has been used by the author for several years in topical therapy of pulmonary disease, primarily tuberculosis, in conjunction with systemic therapy.

The purpose of this paper, therefore, is to confirm the clinical value of combinations of agents in suppressing or preventing the formation of resistant organisms by mutation, to demonstrate the superiority of topical therapy employed in conjunction with systemic therapy, and to suggest the wider applicability of these methods to suppurative lung disorders generally. It is further suggested that the effectiveness of these methods in controlling chronic pulmonary inflammation might also influence the incidence of noninflammatory pulmonary disorders, as reported by Finke.[12]

MATERIALS AND METHODS

Since the introduction of streptomycin in 1947, several hundred patients with suppurative disorders of the lung and pulmonary tuberculosis have been treated in the author's clinic with the several effective antituberculosis compounds.

As suitable combinations of agents have been made available, they have been substituted for single agents; since 1952 the complex streptomycylidene isonicotinyl hydrazine sulfate (Streptohydrazid*) has been used generally in patients suffering from pulmonary tuberculosis.

Our patients have all received topical therapy in addition to the usual systemic administration of antitubercular agents, PAS and isoniazid orally, and Streptohydrazid intramuscularly. Topical therapy consisted of deep inhalation of a mist consisting of a detergent vehicle containing the same antitubercular compounds given systemically.

In the private practice of the author, 34 cases of suppurative lung disease that were treated with combined topical and systemic therapy, using suitable combinations

* The trade name of Chas. Pfizer & Co., Inc., for streptomycylidene isonicotinyl hydrazine sulfate is Streptohydrazid.

of chemotherapeutic agents, have been selected and are presented here as typical of the accomplishment that may be expected with the most effective use of multiple chemotherapy. Patients not receiving multiple chemotherapy both topically and systemically were excluded from the analysis.

Of the 34 patients, the most significant results were achieved with 23 who had pulmonary tuberculosis. In addition there were 9 patients with bronchiectasis and 2 with nontubercular pulmonary abscess, who are presented here as examples of the value of this regimen not only in tubercular lesions but also in other suppurative lung disease.

The diagnosis in each of the 23 patients with pulmonary tuberculosis was confirmed by positive identification of *Myco. tuberculosis* in the sputum or in the culture of sputum or gastric washings. These patients have been observed for one to nine years since they were seen initially.

These cases represent all stages of the disease from newly discovered minimal lesions to large bilateral areas of involvement of many years' duration. The schedule of systemic treatment for pulmonary tuberculosis was standardized at 1 Gm. of streptomycin and 236 mg. of isoniazid three times/week given intramuscularly as Streptohydrazid; an identical amount was given as an aerosol.

Results were evaluated in the patients with tuberculosis by the degree of roentgenographic improvement and by the conversion of sputum. Although there exists some doubt about the reliability of sputum conversion as a test of clinical improvement, a consecutive series of negative cultures is still the single most powerful evidence of successful therapy when supported with obvious clinical improvement.

Nontubercular patients were treated with various combinations of antibiotics both topically and systemically, on shorter and more flexible schedules than for tuberculosis. Results here were evaluated by clinical evidence of improvement.

RESULTS

The concept of topical and systemic administration of combinations of effective agents was originally designed for treatment of chronic unconquerable forms of osteomyelitis and pulmonary tuberculosis, and it is in these diseases that the regimen has proved most successful.

The 23 patients with pulmonary tuberculosis have been followed from one to nine years since beginning therapy. In 16 there has been an opportunity to observe the effects of therapy for three years or longer. In 14 of these 16 there have been more than six consecutive negative cultures of sputum to date. In 1 other patient, who has been treated for three years since the disease was discovered, three consecutive negative cultures have now been obtained. Sputum culture has remained positive in the last patient of the group during three years of treatment, although organisms remain sensitive to streptomycin and isoniazid.

Of the 7 patients observed for less than three years, there have been at least six consecutive negative sputum cultures in 2, disease was far advanced and terminated in death in 2, and positive sputum is still obtained in the other 3. In all our cases, roentgenographic findings were consistent with the persistent negative findings of tubercle bacilli in sputa and gastric contents.

Resistance of the tubercle bacillus to chemotherapy has not been experienced in any of these cases since Streptohydrazid topically and intramuscularly, with oral supplements of PAS and isoniazid, became available for use in multiple chemotherapy. The absence of resistance is attributed to the use of chemotherapeutic agents in combination, and never alone.

Nor has there been, in these cases, any evidence of the undesirable side effects, especially eighth nerve damage, that commonly occur with the use of streptomycin in large doses over long intervals. The absence of such reactions is doubtless due to the lower systemic blood levels made possible by attaining high local concentrations through topical dissemination of the therapeutic agents in the lung.

The remaining patients in this study suffered from suppurative pulmonary disease, either bronchiectasis or pulmonary abscess. These two conditions benefited from topical and systemic attack with multiple chemotherapy, suggesting that surgical intervention may be necessary only in exceptional instances. In these cases a combination of penicillin and streptomycin was employed. Of 9 cases of bronchiectasis, all responded well to treatment. There were no failures in this group. Both of 2 cases of nontubercular pulmonary abscess were likewise benefited.

DISCUSSION

It is apparent from our experience, as illustrated in this report, that the optimal use of systemic and topical chemotherapy in chronic suppurative pulmonary disorders is capable of yielding more consistently good results than are usually obtained in practice.

The phenomenon of drug resistance has not been encountered by us in any patients who have been treated with combinations of two effective agents. This fact is especially significant in pulmonary tuberculosis, where resistance commonly develops to streptomycin or isoniazid alone.

This study, then, comprises a further demonstration that drug resistance in the tubercle bacillus is a function of genetic mutation, and provides rational support for the idea of simultaneous multiple chemotherapy not only in tuberculosis but in any infectious disease that is independently susceptible to two or more chemotherapeutic agents.

The technique of administering effective agents both systemically and topically by means of inhalation of a detergent mist containing the effective agents has a twofold value: It permits high concentrations of active material to reach foci of infection that may be inaccessible by one of the routes of administration. It also makes possible the maintenance of lower systemic concentrations of potentially toxic agents without sacrificing therapeutic effectiveness, since the toxic effects observed with drugs such as streptomycin occur only when the drug is absorbed systemically. This has resulted in the present study in a complete absence of toxic reactions due to streptomycin.

A most important consequence of this study is the realization that this effective regimen is extremely well adapted for widespread use. The equipment necessary for topical inhalation therapy is inexpensive and easily available; the safety of the regimen suggests that its use need not be limited to institutions specialized in tuber-

culosis therapy; and the effectiveness of this therapy compares well with results obtained with chemotherapy in many Veterans Administration hospitals.[1-3]

SUMMARY

1. A representative sample, from the writer's practice, of 23 patients with pulmonary tuberculosis and 11 with other suppurative lung disease were selected for demonstration of principles of chemotherapy.

2. Treatment consisted of combined topical and systemic administration of combinations of suitable chemotherapeutic agents.

3. The results in pulmonary tuberculosis were comparable to those achieved with systemic therapy alone, but in the present study were accomplished with no adverse side effects, and with no development of drug resistance.

4. The results in patients with nontubercular pulmonary infection were superior to those obtained with other methods of therapy.

5. The basis for the superiority of this regimen is presented, and the safety and efficacy of the regimen are emphasized as reasons for supporting its wide adoption.

ACKNOWLEDGMENT

We wish to express our indebtedness to the Medical Department of the Pfizer Laboratories for their cooperation and technical assistance.

BIBLIOGRAPHY

1. Tucker, W. B.: Comparison of the effect of four variables in the antimicrobial therapy of pulmonary tuberculosis. I. Report of the cooperative study of the Veterans Administration, Army, and Navy, April, 1949, to January, 1951, Am. Rev. Tuberc. 72:718 (Dec.) 1955.
2. Tucker, W. B.: Comparative efficacy of three streptomycin and para-aminosalicylic acid regimens of prolonged duration in patients with previously untreated pulmonary tuberculosis. II. An account of the cooperative investigation of the Veterans Administration, Army, and Navy, February, 1951, to January, 1952, Am. Rev. Tuberc. 72:733 (Dec.) 1955.
3. Tucker, W. B., and Livinos, D. G.: Isoniazid, streptomycin, and para-aminosalicylic acid compared as two-drug regimens in the treatment of pulmonary tuberculosis among previously untreated patients. III. An account of the cooperative investigation of the Veterans Administration, Army, and Navy, August, 1952, to September, 1954, Am. Rev. Tuberc. 72:756 (Dec.) 1955.
4. Mitchell, R. S.: The chemotherapy of pulmonary tuberculosis, Am. Pract. & Digest Treat. 6:1855 (Dec.) 1955.
5. D'Esopo, N.: Chemotherapy of tuberculosis in man, J. A. M. A. *154*:52 (Jan. 2) 1954.
6. Committee on Therapy, American Trudeau Society: Antimicrobial therapy of tuberculosis, Am. Rev. Tuberc. 72:408 (Sept.) 1955.
7. Robitzek, E. H.: The selection of anti-microbial drugs for patients of different categories, Dis. of Chest *21*:174 (Feb.) 1956.
8. Grace, E. J.; Bryson, V.; Szybalski, W., and Demerec, M.: Potential danger of isoniazid resistance through failure to use multiple chemotherapy in treatment of tuberculosis, J. A. M. A. *149*:1241 (July 26) 1952.
9. Bryson, V., and Demerec, M.: Bacterial resistance, Am. J. Med. *18*:723 (May) 1955.
10. Finland, M.: Emergence of antibiotic-resistant bacteria, New England J. Med. 253:969, 1028 (Dec. 1, 8) 1955.
11. Grace, E. J.: The use of detergents for topical multiple chemotherapy, XXth Anniversary Surgical Congress, International College of Surgeons, Geneva, Switzerland, May 23, 1955.
12. Finke, W.: Chronic pulmonary disease as a possible etiologic factor in lung cancer, Internat. Rec. Med. & G. P. C. *169*:61 (Feb.) 1956.

The Use of Tetracycline-Vitamin Combination in Acute Infections

H. Marvin Daskal, M.D.

CHICAGO, ILL.

A previous communication[1] reported clinical experience with a preparation combining oxytetracycline and therapeutic doses of water-soluble vitamins in the treatment of a variety of acute infections. The advantages of the antibiotic-vitamin combination over the antibiotic alone were more prompt defervescence, shortened convalescence, and better toleration with fewer and less severe side effects. These observations are in accord with those of other investigators who have reported clinical experience with such combined therapy.[2–5] The present report concerns further experience with a tetracycline-vitamin combination* in the treatment of 100 patients suffering from a variety of acute infections.

MATERIALS AND METHODS

The patients in the present series were 100 adults, 77 women and 23 men, ranging in age from 23 to 85 years. Of these, 72 had various acute infections of the respiratory system, 11 had acute infections of the urinary tract, 11 had acute dermatologic infections, and 6 had acute phlebitis.

The antibiotic-vitamin preparation used was a capsule dosage form for oral administration. Each capsule contained 250 mg. of tetracycline together with the stress formula vitamins recommended for therapeutic use by the Food and Nutrition Board of the National Research Council.[6] The dosage in all cases was 1 capsule four times a day, providing a daily dose of 1 Gm. of tetracycline and the following amounts of vitamins: 10 mg. of thiamine, 10 mg. of riboflavin, 100 mg. of niacinamide, 20 mg. of calcium pantothenate, 1.5 mg. of folic acid, 4 μg. of vitamin B_{12}, 2 mg. of pyridoxine, 300 mg. of ascorbic acid, and 2 mg. of vitamin K.

RESULTS

Therapy was continued in all cases for at least 48 hours after temperature had fallen to normal and all manifestations of infections had subsided. A prompt therapeutic response was obtained in all cases; table I shows the periods of therapy required in the various infections treated.

The number of patients who had any sort of side effects was negligible; 1 patient had moderate nausea and 1 had moderate nausea and diarrhea, neither being bothered seriously enough to require discontinuation of therapy.

SUMMARY AND CONCLUSIONS

A tetracycline-vitamin combination was used in the treatment of 100 adult patients with a variety of acute infections. A rapid and efficient therapeutic response was

* The trade name of Chas. Pfizer & Co., Inc., for the combination of tetracycline and vitamins is Tetracyn-SF.

TABLE 1

Periods of Therapy Required in the Various Infections Treated

Diagnosis	No. patients	Days treated	
		Range	Average
Respiratory Tract Infections			
Upper respiratory infections	19	3–5	4
Tonsillitis	12	3–6	4
Bronchitis	9	3–7	4
Pharyngitis	8	3–5	3½
Pneumonitis	7	5–6	6
Pleurisy	7	3–6	4
Cervical adenitis	5	4–7	5
Otitis media	3	5–6	5
Tracheobronchitis	2	5–6	5½
Urinary Tract Infections			
Cystitis	7	5–6	5
Pyelitis	4	5–7	6
Dermatologic Infections			
Infected dermatophytosis	4	4–6	5
Furuncles	4	3–6	4
Infected sebaceous cysts	3	3–4	3
Phlebitis	6	4–7	5

obtained in all cases. Periods of therapy from three to seven days were sufficient. No significant side effects occurred in any of the patients.

The tetracycline-vitamin combination employed in this study appears to be the broad-spectrum antibiotic preparation of choice.

ACKNOWLEDGMENT

Tetracycline in combination with stress formula vitamins was supplied by Dr. M. William Amster, Director of Medical Service, Pfizer Laboratories, Brooklyn, N. Y.

BIBLIOGRAPHY

1. Daskal, H. M.: Clinical trial of an antibiotic-vitamin combination—oxytetracycline and stress formula vitamins, Antib. Med. 3:33 (June) 1956.
2. Milberg, M. B., and Michael, M., Jr.: Antibiotics and nutrition in infections, Ann. New York Acad. Sc. 63:252 (Oct. 28) 1955.
3. Prigot, A., and Maynard, A. de L.: Fortified broad-spectrum antibiotics as adjuncts in the treatment of surgical infections of the young, the aged, and the debilitated patient, Ann. New York Acad. Sc. 63:230 (Oct. 28) 1955.
4. Zee, M. L.: Evaluation of a new antibiotic-stress vitamin preparation in oral suspension, Antib. Med. 1:661 (Dec.) 1955.
5. Andelman, M. B., and Nathan, L. A.: Combined tetracycline-vitamin therapy in pediatric infections, Antib. Med. 2:45 (Jan.) 1956.
6. Anon.: Therapeutic Nutrition, National Research Council, Food and Nutrition Board, Washington, D. C., 1952, Publ. 234.

The Use of a Sustained-Release *d*-Amphetamine-Amobarbital Preparation in the Treatment of Obesity

Richard P. Shapiro, M.D., and Kenneth I. Michaile, M.D.

NUTRITION CLINIC, PHILADELPHIA GENERAL HOSPITAL

PHILADELPHIA, PA.

The close relationship between obesity and emotional stress has long been recognized,[1–5] and the success of amphetamines in treating obesity has been attributed not only to their anorexigenic action but also to their ability to relieve the depression and anxiety that often characterize the obese patient. Two investigators[6, 7] have found that a *d*-amphetamine and amobarbital combination,* a product whose chief use has been in the treatment of emotional tension,[8–10] is of value as a dietary adjunct in treating obesity of probable psychic origin.

The purpose of this paper is to report on a controlled study on the use of a sustained-release capsule of the *d*-amphetamine-amobarbital combination† in the treatment of obesity. The study was designed to answer the following questions: (1) How do the results achieved by the medication plus diet compare with those achieved by an identical placebo plus diet or by diet alone? (2) What are the incidence and type of side effects resulting from each regimen?

METHOD

The study was conducted on 39 obese patients selected from the Nutrition Clinic of the Philadelphia General Hospital who had failed to lose weight on diet alone. The weights of these patients ranged from 152 to 276 pounds. All were at least 25 to 30 per cent over their ideal weight. Each patient's ideal weight was obtained from the Metropolitan Life Insurance Company's weight tables published in 1951. In addition to obesity, 20 of the patients complained of one or more of the following symptoms: vague aches and pains, irritability, lethargy, emotional instability. Six patients suffered from one of the following complications: sickle cell anemia, esophageal stricture, varicose veins and leg ulcer, gall bladder dysfunction, pelvic inflammatory disease. Two patients were mildly hypertensive; 2 had osteoarthritis.

After receiving complete physical examinations, all patients were first placed on a low calorie diet (1000 to 1400 calories) for periods ranging from 2 to 18 weeks (average, 8 weeks), depending on how well they accepted the diet and responded to it. At the end of the period of diet alone, the patients were placed on one of two coded medications (the active drug or an identical placebo) for eight weeks. At the end of this period the medications were switched. At no time was it known which medication was being administered. The double-blind test in this study

* The trade name of Smith, Kline & French Laboratories for this combination is Dexamyl. Each tablet contains 5 mg. of dextro-amphetamine sulfate and 32.4 mg. of amobarbital.

† Dexamyl Spansule capsules.

was designed to eliminate both the patient's and the investigator's enthusiasm and thus cancel out the psychologic effect of the remedy.

The dose, 1 sustained-release capsule a day, is equivalent to 1 tablet three times a day; however, the capsule is designed to release the medication gradually over an 8 to 10 hour period. The sustained-release capsule was used in order to ensure greater patient faithfulness to the regimen.[11]

Before and after the study, the following laboratory tests were performed on all patients: complete blood count, urinalysis, serum cholesterol and cholesterol ester, and blood sugar tests. In some patients, the protein albumin-globulin ratio was also determined. Blood pressures were taken at each visit.

RESULTS

Weight Results. DIET. The length of time before diet alone proved ineffective varied considerably from patient to patient. Three patients found it impossible to follow the diet for more than two weeks; 15 patients who experienced a more or less satisfactory initial weight loss failed to lose weight after six weeks on diet alone. Twenty failed to lose weight within eight weeks; 1 patient dieted successfully for 18 weeks. As was expected, many patients experienced a sharp initial decline in weight followed by a more gradual loss. Because of the widely varying periods of time for which these patients were on diet alone, it is impossible to arrive at a statistically significant average weekly weight loss for the group.

MEDICATION. The active medication was more effective than the placebo in 21 of the 39 patients, and its superiority was evident whether it was given before or after placebo therapy. Both the active medication and the placebo achieved an equal beneficial effect in 3 patients. The active medication was less effective than the placebo in 5 patients. Ten patients of the entire group did not respond satisfactorily to either medication.

Although the difference between the average weekly weight loss achieved by the active medication and the placebo was statistically significant, it was not a very great one. The average weekly weight loss achieved by the active medication was about one half a pound (0.499 pound); that achieved by the placebo was one third of a pound (0.333 pound).

All laboratory findings were substantially the same both before and after treatment with the active medication. In almost all patients (including the 2 hypertensives), there was a drop in blood pressure coincident with weight loss. The medication had no adverse effect on blood pressure.

The active medication had a pronounced beneficial effect on the mood of 15 patients who were tense, irritable, and depressed. They became much more alert, active, and cheerful. Although the mood improvement coincided with a satisfactory weight loss in 14 of these patients, 1 patient experienced a gain in weight, which seemed to be related to the mild euphoria produced by the active medication.

Two patients credited the placebo with causing a mood improvement. One of these achieved a greater weight loss from the placebo than from either the active drug or diet alone; the other achieved a greater weight loss from the active drug than from diet alone or placebo.

No serious side effects were noted. While on the active medication, 9 patients complained of thirst, 4 of jitteriness, 1 of both thirst and jitteriness. While on the placebo, 2 patients complained of thirst, 1 of jitteriness.

DISCUSSION

The results in these patients quite clearly illustrate the extreme difficulty of bringing about effective weight reduction in the grossly obese person by the use of diet alone. All these patients failed on the diet after their initial enthusiasm wore off, and all needed some support other than diet.

The partial success of the placebo indicates that for many patients the mere ritual of taking *some* medication enables them to be more faithful to diet; however, the significant difference in the average weight loss obtained by the placebo and the active medication indicates that the *d*-amphetamine-amobarbital combination may be an effective anorexigenic agent. The active medication's superiority assumes more significance when one takes into consideration that even when the placebo was given early in the study (when weight loss might be considered easier to achieve), it was still inferior to the active drug.

More impressive than the medication's anorexic action was its ability to relieve many of these patients of vague, yet troublesome, psychosomatic complaints. The cheerfulness and physical well-being experienced by these patients usually, but not always, coincided with a loss in weight.

The results of this study indicate that the majority of grossly overweight patients need therapy other than diet to achieve a significant weight loss, and that the sustained-release *d*-amphetamine-amobarbital combination is of particular value in treating nervous, depressed patients.

SUMMARY

A double-blind study was carried out on 39 grossly obese patients who had failed to lose weight on diet alone in order to test the efficacy of a sustained-release *d*-amphetamine-amobarbital capsule. The active medication, or an identical placebo, was given for eight weeks, after which the medications were switched. Patients were seen biweekly. Complete laboratory tests were made before and after the study.

Both the placebo and the active medication caused 29 of these 39 patients to lose weight. The active medication was significantly better than the placebo in 21 patients, no better in 3, and less effective in 5. The average weekly weight loss on the active medication was about one half of a pound; on the placebo, one third of a pound. The active medication resulted in the marked alleviation of depression, anxiety, and/or other psychosomatic symptoms. Four patients complained that the active medication made them jittery; 9 complained of thirst; 1 complained of both thirst and jitteriness.

CONCLUSIONS

1. Many grossly obese patients need therapy other than diet to achieve a satisfactory weight loss.

2. Placebo therapy can achieve a limited success in most of these patients.

3. The sustained-release *d*-amphetamine-amobarbital capsule is a safe, effective anorexigenic agent and is of particular value in alleviating the emotional tension and psychosomatic complaints suffered by many obese patients.

BIBLIOGRAPHY

1. Bayles, S., and Enough, J.: Emotional factors in obesity, J. Am. Dietet. A. *26*:430–434 (June) 1950.
2. Freed, C.: Psychic factors in the development and treatment of obesity, J. A. M. A. *133*:369–373 (Feb. 6) 1947.
3. Schick, A.: Psychosomatic aspects of obesity, Psychoanalyt. Rev. *34*:173–183 (April) 1947.
4. Burch, H.: Psychological aspect of obesity, Bull. New York Acad. Med. *24*:73–86, 1948.
5. Newburgh, L. H.: Obesity, Arch. Int. Med. *70*:1033–1096, 1942.
6. Roberts, E.: The treatment of obesity with an anorexigenic drug, Ann. Int. Med. *34*:1324–1330 (June) 1951.
7. Rosenberg, P.: The use of mood ameliorating agents in the treatment of psychogenic obesity, Am. Pract. & Digest Treat. *4*:818–820 (Dec.) 1953.
8. Drayton, W., Jr.: Recognition and management of the depressed mental state, Pennsylvania M. J. *54*:949, 1951.
9. Grahn, H. V.: The depressed patient: management with the aid of a new medication, Am. Pract. & Digest Treat. *1*:795, 1950.
10. Grahn, H. V.: Sedation without depression in the management and treatment of the aged, Am. Pract. & Digest Treat. *4*:540, 1953.
11. Jenkins, B. W.: Are patients true to t.i.d. and q.i.d. doses? GP *9*:66–69 (June) 1954.

Sixth International Congress of Otolaryngology

The Sixth International Congress of Otolaryngology will be held in Washington, D. C., from Sunday, May 5, through Friday, May 10, 1957. Selected subjects for the Plenary Sessions will be: (1) Chronic Suppuration of the Temporal Bone; (2) Collagen Disorders of the Respiratory Tract; (3) Papilloma of the Larynx. Outstanding internationally recognized authorities will open the discussions on each of these subjects. Communications of two types are invited: Contributions to the discussion of the selected subjects; speakers limited to five minutes. Original papers; speakers limited to 15 minutes. All communications should be in one of the official languages: English, French, German, or Spanish. Motion pictures will be shown continuously except during Plenary Sessions. There will be both scientific and technical exhibits. Those wishing to submit contributions to the program should communicate with the General Secretary.

The subscription for Members (physicians) is $25.00 U. S. A. This includes the privilege of attendance at all official Congress meetings except the banquet, for which an additional charge will be made. Other persons accompanying Members may be registered as Associates at a fee of $10.00 U. S. A.

All communications should be addressed to the General Secretary, Paul H. Holinger, M.D., 700 No. Michigan Ave., Chicago 11, Ill., U. S. A.

The Action of Salicylate as Related to Pituitary-Adrenal Function*

Charles H. Eades, Jr.,† and J. Stanton King, Jr.‡

DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF TENNESSEE
MEMPHIS, TENN.

GENERAL BACKGROUND

The mechanism whereby acetylsalicylic acid and sodium salicylate are efficacious, indeed almost specific,[1, 2] in alleviating the symptoms of rheumatic fever and certain other of the arthritides was, and largely still is, unknown. Nevertheless, the clinical opinion has persisted that the beneficial effects of the salicylates§ are more pronounced than can be accounted for simply on the basis of their analgesic and antipyretic properties alone.

Significant developments in knowledge concerning the mechanism of action of salicylates in the rheumatic diseases awaited some key discoveries that have been made, chiefly during the last decade, in an area that superficially might appear to be only remotely related to SAL§ action. This was the field of the chemistry and physiology of the adrenocorticotropic and adrenocortical hormones. A concept of one mechanism of SAL action has emerged as a corollary to this main line of fundamental investigation, and is the subject of this review.

OBSERVATIONS CONCERNING THE EFFECT OF SALICYLATE ON THE PITUITARY-ADRENAL SYSTEM

In 1950, several years after the present idea of the functional mechanisms of the pituitary-adrenal axis had begun to crystallize, it was first suggested by Calesnick and Beutner[3] and experimentally indicated by Blanchard et al[4] that SAL seemed to affect the pituitary-adrenal system and that their clinically observed effects might be, in part, a manifestation of their effects on this system. These papers appeared about a year preceding a similar suggestion by Cochran et al,[5] made on the basis of clinical observations. Six independent investigations[6–11] promptly confirmed and considerably extended the work of Blanchard et al.[4] Since that time a variety of other observations have almost consistently tended to support this conception.

The development of the concept will be presented by making a comparison be-

* This review is adapted from a thesis submitted by J. Stanton King, Jr., in partial fulfillment of the requirements for the degree of Doctor of Philosophy, University of Tennessee, 1954.

† Present address: Research Laboratories, Mead Johnson & Co., Evansville, Ind.

‡ Present address: Research Laboratory, S. E. Massengill Co., Bristol, Tenn.

§ In the subsequent presentation, the abbreviation SAL will be used to designate acetylsalicylic acid and /or the salts of salicylic acid used in internal medicine, most commonly sodium salicylate. Any effect produced by acetylsalicylic acid is reproduced qualitatively by the latter, so far as the authors are aware.

tween certain effects of SAL as compared with cortisone and ACTH.* Since reviews are available on many of the related subjects to be discussed here, only key references will be given when they are appropriate, rather than attempting a prohibitively comprehensive documentation. In general, reference will be made only to the most recent publication on the same problem by any one author or group of authors. A more complete bibliography can be found elsewhere.[12]

Clinical Evidence. Rheumatic Fever. SAL, in high dosages, has been favorably compared[1, 2, 13–17, 153–156] with cortisone and ACTH in the treatment of rheumatic fever in studies where a comparison has been made by the same workers. Many of the remissive symptoms following SAL therapy are the same as with hormonic therapy (see below). There is a "rebound" of the signs and symptoms if SAL is prematurely withdrawn, together with a recrudescence of inflammation.[13] These same observations have been made with cortisone or ACTH.

Rheumatoid Arthritis. SAL has been used so classically in the treatment of rheumatoid arthritis that little comment would seem necessary here, although the beneficial effect of small doses may reside chiefly, if not solely, in its analgesic properties.

It is of considerable interest here that the same high blood levels of SAL reported by Coburn[15] and confirmed by others[2, 16, 17] to be effective in alleviating rheumatic symptoms are also requisite to maximal adrenal ascorbic acid (AAA) depletion in rats.[6–12] Moreover, blood SAL levels are directly related to the AAA decrease.[8, 18–20] Camelin et al[21] are apparently the only workers to dispute the necessity for such high blood levels in successful therapy.

The use of ACTH and cortisone in this disease has also been so widely reported, reviewed, and publicized in the medical and lay press that their efficacy is widely appreciated. Many reviews and bibliographies are available confirming this.

In Great Britain, a particularly thorough and extensive clinical study[22] has been reported that had as its purpose the comparison of acetylsalicylic acid and cortisone therapy in the treatment of rheumatoid arthritis. Although certain criticisms of the study have appeared, the conclusion which is consonant with those of less definitive studies, seems warranted that these two agents are approximately equally beneficial.

Other Diseases. SAL has been tested to determine its clinical effectiveness in other diseases, among them those grouped under the rubric "connective tissue" or "collagen" diseases, and certain other maladies for which adrenocortical hormonic treatment is also effective. SAL has been reported to be helpful in osteomyelitis,

* In this paper, the term "ACTH" will, by definition, represent only that agent (or agents) secreted by the adenohypophysis and producing a decrease in adrenal ascorbic acid concentration. This will avoid the current question concerning the possibility of a multiplicity of adrenotrophic hormones, each exerting a specific effect (e.g., on eosinophils, ascorbic acid, or adrenal weight).

Since there has thus far been no important action of ACTH established other than its trophic action on the adrenal cortex, this compound and cortisone may be considered together, in a cause-and-effect relationship, in comparing certain results produced by SAL with similar effects produced by cortisone and/or ACTH. Cortisone is the steroid used for comparison here. It is now believed that hydrocortisone (Kendall's compound F) is the steroid playing the most important glucocorticoid role in the human being, but it has only recently been available for experimental use.

polyarticular rheumatism, ankylosing spondylitis, fibromyositis, lupus erythematosus, scleroderma, infective endocarditis, periarteritis nodosa, psoriasis, asthma, and serum arteritis.

By comparison, Coste and Lacronique[22] reported that a variety of proposed therapies, other than with cortisone, ACTH, or SAL, ended in failure as a treatment for ankylosing spondylitis or rheumatoid arthritis.

Analgesic Properties. The use of SAL, ACTH, and cortisone to relieve rheumatic joint pain is now standard practice. However, none of these is a general anesthetic, and neither cortisone[24] nor acetylsalicylic acid[24–26] elevates the pain threshold in man. The analgesic properties of SAL are also limited to pain arising from the integumental system.

Antipyretic Properties. Despite contrary reports, the antipyretic effect of ACTH and cortisone seems well established; the same is true of SAL.

Ocular Anti-inflammatory Effects. ACTH and cortisone have ocular anti-inflammatory effects. Gifford[27] and others report the same to be true for systemically administered SAL.

Cushing's Syndrome. Overdosage of ACTH or cortisone produces symptoms of hyperpituitarism or hyperadrenalism. SAL in large doses has been observed to do the same.[5, 28]

Catabolic Effect. The nitrogen balance of experimental animals[29] or human beings[30] on cortisone or ACTH therapy becomes negative.[31] This is generally supposed to be a result of increased protein catabolism, i.e., a consumption of the so-called "protein reserves," particularly thymolymphatic tissue.

Although the extensive literature on this point is very contradictory, it has been repeatedly observed that SAL causes a similar catabolic effect. Microbiologic measurement of the individual amino acid excretion (and amino N^{32}) after either ACTH, cortisone,[12, 33–35] or SAL[12, 36] therapy in the human being shows some marked increases over the normal levels.

Uric Acid Excretion. There is an increased urinary uric acid excretion after ACTH or cortisone or SAL therapy, as well as an increase in the uric acid/creatinine ratio. This uricosuric action is probably the chief pathway for benefit from therapy of gout with either ACTH or SAL. The uricosuric action of SAL is blocked by hypophysectomy.[37]

Sedimentation Rate. The increased erythrocyte sedimentation rate in rheumatic fever and rheumatoid arthritis patients is significantly decreased after treatment with ACTH and cortisone. The same has been reported after SAL treatment[15, 39–41] with doses that give plasma levels having no in vitro effect, an increase in sedimentation rate occurring again upon the discontinuation of SAL.[40] The structural specificity of this action has been examined.[41]

Skin Sensitivity Reactions. ACTH, cortisone, and SAL block both the Arthus phenomenon[44–46] and the Shwartzman reaction to bacterial antigen.[44, 47]

Serum Vascular Disease. Eosinopenia can be expected after administration of ACTH or cortisone. A similar change has been noted[25, 48–51] after moderate to high doses of SAL. Pasqualini[50] and Roskam and Van Cauwenberge[51] have shown in human beings that the degree of eosinopenia is directly proportional to the degree

of salicylemia. This effect of SAL has been more thoroughly studied in rats and guinea pigs.[25, 48, 52, 53, 78] In man, a 50 per cent decrease in the number of circulating eosinophils occurred four to six hours after the oral administration or four hours after the intravenous administration[51] of SAL; this is comparable to the four hour period required for its appearance after the injection of ACTH or cortisone. Meade and Smith[54] and Comulada et al[55] failed to observe this effect with SAL and regarded this as evidence that SAL does not cause an increased output of cortical steroids from the adrenal. The explanation for their negative results may lie in the fact that the eosinophil count after oral administration was followed for only four hours. At this time the alteration is usually insignificant, as Roskam et al[56] pointed out. These authors attribute the additional time required for the eosinopenia to occur with oral SAL to the slowness of absorption of the requisite amounts of SAL from the gastrointestinal tract. By comparison, in this same paper they showed that the uric acid/creatinine ratio was observably altered two hours after the ingestion of SAL.

Kelemen and Majoros[49] emphasized the necessity of high dosage of SAL before the eosinopenia is quite pronounced in human beings. Kelemen[57] has reviewed several of the factors that seemingly affect the number of circulating eosinophils. He notes that SAL caused significant eosinophilia in adrenalectomized rats[57] or rats pretreated with Dibenamine,[52] while no such effect was observed with cortisone. Eosinophilia also occurs in human patients after adrenalectomy or 12 to 18 hours after such operations as cholecystectomy successive to eosinopenia.[58]

This criterion of cortical activity is poorly understood at the present time. For example, several nonsteroid substances[59, 60] have also been found to elicit eosinopenia. In addition, there are such enigmatic observations as the induction of eosinopenia by epinephrine in completely adrenalectomized human subjects,[61] a phenomenon obviously unexplained on the basis of any action by adrenocortical hormones.

Coadministration of Hormones and SAL. Numerous reports of the coadministration of cortisone and SAL have appeared.[51, 62–67] The results were uniformly consistent with the conclusion that a synergistic, or at least an additive, action had occurred. The benefits of such a combination are evidently mutual, since Montuori and Balla[68] demonstrated that cortisone decreases the acute toxicity of SAL.

Evidence Derived Principally from Experiments on Animals. Adrenal Ascorbic Acid (AAA). ACTH causes a specific[69] decline in AAA concentration while cortisone does not. SAL has repeatedly been found to produce a similar fall in AAA in the intact rat.[8–11, 18, 25, 53, 55, 70, 71] The time relations are about the same with injected ACTH, but recovery is slower with SAL, undoubtedly because it is present in active form in the blood stream longer than the rapidly inactivated ACTH. The depletion by SAL is completely prevented by hypophysectomy.[10, 11, 18, 37, 48] Some workers[72, 73] have found a decrease even in hypophysectomized rats; the reason for this disagreement is not clear at present, but is possibly explained by incompleteness of the operation. AAA depletion is not produced simply by a change in the chemical environment of the adenohypophyseal cell, as is shown by the inactivity of a variety of compounds injected in high doses.[18, 74, 75] These data indicate that

the effect of SAL under discussion is a specific* pharmacologic action. Done et al[76] have found that AAA response does not necessarily reflect the plasma steroid levels. For example, they found that all dihydroxybenzoic acids produced marked elevations, those with one of the -OH groups in the ortho position having an even greater effect of this kind than salicylate. Further work will be necessary to interpret properly these interesting findings.

Adrenal Cholesterol Concentration. ACTH administration also causes a diminution in adrenal cholesterol concentration.[69] The same decline is observed after the administration of SAL,[52, 55, 71] but is abolished by hypophysectomy. One set of workers reports a failure to observe significant depletion after SAL,[55] an inappropriate time interval being apparently responsible. Bach et al[28] reported that serum cholesterol rises, after an initial drop, following SAL therapy, as it does after ACTH therapy. Stenger et al[77] report that adrenal cholesterol and adrenal ascorbic acid may be independently varied, which confuses the interpretation of these measurements.

17-Ketosteroids. The urinary excretion of 17-ketosteroids is increased in human beings after ACTH and decreased after cortisone, if the level is initially high. Bonati et al[78] and others[80] found a decrease in the 17-ketosteroid excretion after SAL. Van Cauwenberge and Heusghem[82] found that 17-ketosteroid excretion in rheumatic fever patients was variable after acetylsalicylic acid therapy. Cochran et al[5] and Henly[84] found no significant alteration in 17-ketosteroid excretion consequent to SAL therapy.

Glucocorticoids. Several workers[79–83] found a significant increase in the level of reducing steroids of the blood and/or urine of patients and experimental animals treated with SAL, as is found after cortisone and ACTH. This increase was not found with hypophysectomized or adrenalectomized guinea pigs.[81]

By contrast, others[84–87] have found no effect of high dosages of SAL on plasma and/or urinary adrenocortical steroids. Rheumatic fever patients seem peculiarly unresponsive.[88] More studies on this subject would be highly desirable, since the pituitary stimulation presumably effected by SAL could have its beneficial action more or less nullified by a concomitant and equivalent increase in the "consumption" of cortical hormones by the tissues.

Carbohydrate Metabolism. A significant anomaly in the comparison of the effects of cortisone and ACTH with those of SAL has been their diametrically opposite effects on carbohydrate metabolism, in contrast to the general parallelism found in other types of observations.

It has been established that cortisone or ACTH administration induces an increase in liver glycogen concentration and a decreased glucose tolerance. SAL administered to rats[55, 89] and mice[90] causes a pronounced diminution in liver glycogen, and in normal rats does not elevate blood or urinary glucose. Ingle[91] observed that acetylsalicylic acid reduces glycosuria in diabetic rats. Ingle and Smith and their associates have studied this problem. It has been found that SAL mitigated a cortisone-

* By "specific" is intended "possessing this property to a more marked degree than would be expected merely from its toxicity or from comparison with the degree of similar activity of analogous or homologous compounds."

induced glycosuria and hyperglycemia in high carbohydrate-fed[92] or alloxanized[93] rats. In adrenalectomized rats, the liver glycogen concentration was depleted after a four to six hour fast; it increased if cortisone was administered, but was markedly depleted if cortisone and SAL were given together. Insulin is more toxic after SAL administration,[94] whereas ACTH inhibits insulin hypoglycemia.[95]

That there is no direct relationship of these effects of SAL to its pituitary-adrenal action is shown by the persistence of the effect of SAL on liver glycogen after hypophysectomy,[55] and also by the work of Ingle et al[96] using partially depancreatized, carbohydrate-fed rats. Glucosuria was suppressed by acetylsalicylic acid, whether or not the rats were adrenalectomized. Smith has furnished a partial explanation of this paradox; he found SAL to delay gastric emptying[97] and obtained evidence for the later participation of adrenal cortical stimulation in the effects on liver glycogen[98] and blood glucose[99] and for an increased intestinal glucose absorption induced by salicylate.[100]

Anaphylactic Shock. Although there are negative observations, mortality from anaphylactic shock is reportedly decreased by cortisone and ACTH,[101, 102] as it was by SAL.[103, 104] SAL behaved as did cortisone in experimental hypersensitivity reactions.[105]

Permeability Effects. ACTH or cortisone apparently inhibits the spreading action of hyaluronidase, although there are some negative results recorded concerning this.

SAL diminishes synovial permeability in guinea pigs, according to Thieblot et al.[106] In rabbits, the spreading effect of hyaluronidase was markedly inhibited by SAL,[107] but it had no effect on hyaluronidase either in vitro[108] or in vivo after hypophysectomy or adrenalectomy.[109] No correlation could be found between the direct degree of antihyaluronidase activity of SAL and related phenolic compounds and their indirect action in the body.[111] Kelemen and associates[52, 57, 112] found that SAL inhibited the action of hyaluronidase injected into the joints of rats. Bywaters et al[113] showed that the reconstitution of the dermal barrier after hyaluronidase injection is slow in rheumatoid arthritis and rheumatic fever patients, but is returned to normal by SAL, cortisone, or ACTH medication. Several workers[114, 115] have observed an inhibition of hyaluronidase by SAL in human beings. Van Cauwenberge and LeCompte[116, 117] have published work indicating that, under carefully controlled conditions, neither ACTH, cortisone, nor SAL has any noteworthy antihyaluronidase activity. Bianchi[118] found SAL to diminish synovial permeability, while cortisone had an uncertain effect.

Kelemen[112] found that the antihyaluronidase properties of SAL, and also its antihistaminic properties, are largely independent of the pituitary-adrenal system. ACTH did not give protection in the "limb-edema" test against hyaluronidase action in rats, whereas SAL and cortisone acetate did. (This appears to be a "permissive" action of cortisone.[112]) Moreover, experiments with barbiturate-anesthetized rats showed that both the antihyaluronidase and the antihistaminic properties of SAL could be demonstrated without eliciting the usual signs of adrenal stimulation, and vice versa. The hyaluronidase protection by SAL was inhibited by adrenal demedullation, while ACTH stimulation remained unimpaired.

Histologic Observations. The histologic and gross morphologic changes in the lymphatics, thymus, and spleen after SAL treatment of various laboratory animals parallel those produced by the administration of cortisone or ACTH[4, 43, 46, 119] or by the "alarm reaction" by Selye. No obvious alteration in rat adrenal weight or histologic appearance is produced by three week SAL administration (200 mg./Kg.).[12] The adrenal cortical atrophy produced by cortisone is prevented by either SAL or ACTH.[120, 121]

Anti-inflammatory Effects. According to Selye,[122] ACTH and cortisone inhibit the simulated arthritis induced by the intra-articular injection of formalin. Analogously, SAL, but none of several other analgesics tried, reduces joint swelling produced by the intra-articular injection of silver nitrate.[123] Guerra[124] was successful in showing that acetylsalicylic acid reduces the swelling in the joints of formalin-arthritic rats. Bacchus and Bacchus[125] confirmed these results and found that they did not occur in similarly treated adrenalectomized rats. Rivi[52] also reported that large doses of SAL gave a distinct protective action against the arthritic symptoms resulting from the intra-articular injection of formalin into rats. Both SAL and cortisone were found to be effective in passive Arthus arthritis.[126]

The inflammatory action of chloroform on human skin is inhibited by either ACTH or SAL.[127] The SAL appears to act both by a direct mechanism and through pituitary-adrenal stimulation. The antiphlogistic actions of cortisone and salicylate are summated when the two are coadministered,[128] as measured by the "granuloma pouch" technique.

Hormonic Blockade. Hetzel and Hine[11] have shown that the previous administration of cortisone partially blocks the depleting effect of SAL on AAA, an observation confirmed and quantitated by Cronheim and Hyder.[129]

Irradiation Resistance. Resistance of mice to roentgen radiation is increased by the injection of ACTH[130] or of SAL[131] beforehand.

Stimulation of ACTH. A rise in the titer of circulating ACTH following SAL administration to rats has been demonstrated.[132]

Effect on Antibody Titers. Daily treatment with SAL reduced the concentration of circulating antibody in rats infected with *Trypanosoma lewisi*.[133] ACTH and cortisone have been reported to do the same sort of thing.[134, 135]

Effect on Growth. Chronic salicylism (200 mg./Kg./day) produced growth rate subnormalities in growing rats only after about 17 days,[12] similar to the effect of cortisone administration.

ACTION OF COMPOUNDS RELATED TO SAL

While these observations accumulated, the suspicion that SAL stimulates the pituitary-adrenal system, and thereby exerts part, at least, of its antirheumatic effects, grew correspondingly stronger. As the supply of information on the subject increased, there was a renaissance of interest in a formerly passive and almost purely arbitrary phase of inquiry; namely, the similar trial of compounds chemically related to SAL[12, 18, 55, 74, 136–140] to see if such compounds would exert a similar and possibly more effective action. It was also hoped that the unpleasant side effects

that usually occur with the higher dosages of SAL that are clinically effective could be obviated by the substitution of some related compounds.

Much research consequently has been done in an attempt to correlate structure with antirheumatic activity, as reflected in AAA and/or adrenal cholesterol decreases in rats after administration of analogues and homologues of SAL. As mentioned previously the recent work of Done et al[76] and Stenger et al[77] necessitates a re-evaluation of these criteria. A survey of the results[12] shows that, while certainly not unique in exhibiting the effect, SAL is one of the most potent of the drugs tested. In rats, 75 mg./Kg. produces an unambiguous decrease in AAA. When considering the consistency of the results of one group of workers as compared with those of another, it must be taken into account that there are certain variations in technique among workers that affect the results (e.g., time relations, the injection route used). Moreover, a depletion of AAA will be produced by *any* such drug if a toxic dose is given. Thus, in interpreting the results of such experiments, the AAA decrease should not be assigned as a specific action if a near-lethal dosage is required to produce it; this is a rather common error.

An interesting side light to this investigation was the controversy concerning the degree of clinical efficacy of gentisic acid in improving rheumatic disease, presumably via a direct antihyaluronidase effect.

This dilemma began to be resolved when Roseman and Dorfman[141] noted that the more nearly pure the gentisic acid used, the less antihyaluronidase action it exhibited in vitro. It has been concluded that an impurity in the gentisic acid was responsible for the positive results. The clinical impotency of pure gentisic acid is paralleled by its relative inactivity with reference to AAA[18] and by its rapid excretion.[142]

Reid et al,[128] assuming that the antirheumatic effect of SAL might be related in some way to its well recognized chelating ability, due to the ortho-hydroxy grouping, reasoned that resorcylic acid (2,5-dihydroxysalicylic acid), with two such ortho groupings, should be more effective than SAL. They found that while smaller doses of resorcylic acid appeared clinically to be more effective, they were also more provocative of undesirable side reactions. It has been found by various workers, including Reid, that resorcylic acid does not have a marked AAA-depleting effect.

Glycine may have a specific supplementing action on the antirheumatic effect of SAL.[12, 75, 143–145]

OBSERVATIONS CONCERNING THE MECHANISM OF THE EFFECT OF SAL ON THE PITUITARY-ADRENAL SYSTEM

The Nature of the Active Structure. It was conceivable that the active compound was not actually SAL itself, but instead some metabolite of it. On testing, all of them were found to be less active (on AAA) in chemically equivalent doses than was SAL itself.

Pharmacodynamics of the Pituitary-Adrenal Stimulation by SAL. The experiments with hypophysectomized rats that were described here have made it clear that SAL does not directly affect the adrenal cortex, but instead appears to act, directly or indirectly, on the anterior pituitary.

Certain observations[69, 146–149] suggested that the nervous system was involved in responses of the pituitary-adrenal system and that it might also be involved in the response of this system to SAL administration. The first experiments designed to investigate this possibility were reported by Van Cauwenberge and Betz.[150] They presented data showing that rats anesthetized with diallyl barbituric acid gave the same nearly negative response to 50 or 500 mg./Kg. doses of SAL. Cronheim and Hyder[129] showed that the depletion in AAA concentration produced by SAL may be blocked by deep, but not by light, barbiturate anesthesia. Direct local anesthesia of the hypothalamic area achieved the same result.[12]

Although these results suggested that epinephrine stimulation might also be involved, it cannot be an important factor, since Kelemen et al[151] observed that the AAA-depleting effect of SAL is still manifested in rats subjected to adrenal demedullation.

The sympatholytic drug, Dibenamine, produces AAA depletion in rats.[146] However, according to Van Cauwenberge,[152] doses of Dibenamine hydrochloride that do not per se cause a statistically significant depletion of AAA or cholesterol or eosinophils did inhibit the previously very significant effect of large doses of epinephrine on these levels. Under the same conditions, the action of SAL was unaffected by Dibenamine.

While these latter experiments also appear to divorce epinephrine from a role in the effect in question, it is still not clear as to just what has occurred. Dibenamine would not be expected to inactivate epinephrine directly.

SUMMARY

A review of the clinically and experimentally observed similarities of and differences between the effects of ACTH and cortisone as compared with those of salicylate (SAL) and related compounds has been presented. The almost consistent parallelism indicates stimulation of this axis as one mode of SAL action. The mechanism whereby SAL accomplishes this effect is still largely obscure but apparently involves the central nervous system without an obligatory role of epinephrine.

(Please turn to page 679 for Bibliography.)

On the Psychology of Symbolism in Oriental Rugs*

Félix Martí-Ibáñez, M.D.

PROFESSOR OF HISTORY OF MEDICINE, NEW YORK MEDICAL COLLEGE, FLOWER AND FIFTH AVENUE HOSPITALS, AND EDITOR, INTERNATIONAL RECORD OF MEDICINE AND GENERAL PRACTICE CLINICS, NEW YORK, N.Y.

THE LANGUAGE OF SYMBOLS

"*In the beginning was the symbol . . . .*" The symbol was the very first means devised by man to express himself. Symbolism heralded all human languages. The language of symbols is the most universal in space and is the one that has best survived through time. A symbol is a veritable fossil of human thought.

Man began creating symbols as soon as his brain awakened to the realities of the world about him. Scorched by prehistoric suns, shivering with cold in his cave during the endless nights of the Ice Age, primitive man lived in panic over two fears that he had continually to face: loneliness and death. At the bottom of his fear of loneliness lay his reproduction instinct, which demanded companionship; underlying his fear of death was his instinct of self-preservation, which warned him that only through health and strength could he conquer death.

To fight these terrors, man evolved an animistic interpretation of the universe and peopled it with intelligent forces. Thus animistic religions began, and the first myths, projections of man's hopes and fears, were born. In the course of time, myths were succeeded by legends—expressions of History distorted by the imagination. Myths were collective hallucinations; legends were the delusions of peoples. The first were perceptions without object; the latter, with object. Both still are the most archaic and spontaneous form of expression of all peoples.

A symbol has been defined as "something that represents and hides something else." The word "symbol" stems from the Greek *symballein*, meaning to bring together, to join. A symbol is something whose outer appearance conceals a much broader inner meaning. It is a nodal point from which different rays of meaning emerge. It has a *conventional* meaning: the relationship existing between any object and the word that designates it; it has an *accidental* meaning: an object may affect a happy or a sad connotation depending on a person's experience with that object; and it has a *universal* meaning, the most important of all, for symbols are similar in all ages and among all peoples.

Symbolic language is not only the most ancient but also the most universal of all languages. It was used by primitive man at the dawn of History: it is still used by modern man in his dreams, by the child in his fancies, by the neurotic in his rituals, and by the artist in his creations. The common denominator of all people who resort to the language of symbols is a creative compulsion to extract from the subconscious a wide variety of images with which to disguise realities bearing a deep universal

* This is a new and considerably enlarged article especially written for this journal, based on the author's Foreword to the book *The Hidden Language of Oriental Rugs* by Harry Raphaelian.

meaning. By analyzing these symbolic images, it is possible to dig into the unconscious of peoples, where their mental archetypes are buried in darkness and, like precious stones exposed to the light, can be made to sparkle only when exposed to a quick flash of consciousness.

Graphology was born before writing, with the simplest of human gestures—a motion of the hand, which is the first gesture made by the newborn babe as if greeting the world, and the last made by the dying as if bidding the world good-by. The finger of primitive man scratching on the sand of his cave—on the sands of time as it were—gave rise to subsequent graphism, just as his dreams, fancies, fears, and hopes gave rise to myths, legends, and fables.

Later, in his daydreams and night dreams, in his neurotic rituals and his artistic creations, man individually continued to use the same symbols that occurred in the collective language of peoples. Symbolic language is invaluable for studying the psychology of peoples as well as of man individually. Man's dreams today, whether in New York or in the African jungle, are the same as man's dreams in the times of the Egyptian Pharaohs or the Roman Caesars.

Time never stops in its endless march, but man, as Goethe observed, remains the same. This immutability of the human being, modified only by such biologic differences as are imposed by ecology and evolution, is also characteristic of symbolism, to which man has always resorted to hide those subconscious desires and terrors that are the quintessence of his being.

Man has always used symbolism in his thinking, in his writing, in all his creative endeavors. Symbolism was the basis of the so-called primitive magic thought that governed the mind of ancient man. It was the basis of the ideographic writing of many Oriental peoples, which has so amazingly survived to our day, as it was also the basis, subtly distorted and disguised but rediscovered by modern graphology, of Western writing. Even punctuation marks can reveal something of the collective soul. For instance, the Spanish language is perhaps the only one in the world with two question marks (¿?) and two exclamation marks (¡!), placed respectively at the beginning and at the end of a question or an exclamatory sentence, as if to translate the tremendous emotional capacity of the Spanish people when curious or surprised.

Symbolism is the basis of most modern art, and it has also exercised a great influence on the ornamentation of many objects of daily use.

The "lost language" of symbols has represented throughout history the way of all peoples of expressing their repressed fears and desires. Harold Bayley, in his book *A New Light on the Renaissance* (1909), formulated the theory that from 1282 (when they were introduced) to the second half of the eighteenth century, watermarks represented an uninterrupted coherent chain of emblematic symbols. Such symbols were, so to speak, fossilized or crystallized thoughts; they preserved in the sanctuary of a cryptogram the aspirations and traditions of many of the mystical and puritanical sects that abounded in Europe in the Middle Ages. They are indubitably historico-psychologic documents of great importance.

Through the symbolism in watermarks we know that the art of papermaking was introduced in Europe by Protestant sects—the Albigensians and Vaudois in France and the Cathari or Patarini in Italy—antedating the Reformation. These sects con-

tinued to exist secretly for several centuries after they were excommunicated and outlawed by the Pope. An identical origin may be ascribed to the symbolic decorations used by printers in the Middle Ages. Printers, papermakers, and other such artisans were the precursors of the Renaissance, the period when symbolism became more manifest in art.

The same may be said about symbolism in Oriental rugs. Like the fossil that imprisons within its bed of stone the skeleton of a fish or the petals of a prehistoric flower, the symbols in rugs preserve many a dream and fear of the ancient peoples who fashioned them.

Onto the objects he creates, man always projects a varied collection of symbols representing the psychologic harvest of many centuries. All art handed down to us, however crude or humble, is encrusted with symbols in which the great fears and preoccupations of many generations palpitate. This is particularly true of Oriental art, for symbols have played a more vital part in the Oriental than in the Western mind, and they have been used with bounteous hands in Oriental art, and particularly in rugs, of which Sargent and Holmes have said: "There is more art in a great Oriental rug than in any picture of any period."

ON THE HISTORY AND PHILOSOPHY OF RUGS

If the value and importance of an object are based on the multiplicity of its uses and its historical tradition, then the rug indubitably outshines any other object used by man for utilitarian or ornamental purposes. For no other object has as many uses or has as faithfully kept man company in his cavalcade through History as the rug.

The origin of rugs is lost in prehistoric mists. Felt rugs (the Pasyrik rugs of the Altai Mountains) have been found that are 30,000 years old and belong to the Paleolithic Age. But no one has thoroughly investigated the origin of rugs.

We can imagine how rugs came into being when prehistoric man, crouching on the muddy floor of the cave he shared with the snake and the frog, felt the necessity of protecting his body from dirt, cold, and dampness. Perhaps he began by covering the ground with leaves and branches, and then tried braiding roots into a mat to keep out the cold and humidity. Later, during the interminable prehistoric nights, women wove thick mats of vegetable fiber. Thus, perhaps, the first rugs were born. The vegetable rug was undoubtedly cleaner and more practical than animal skins, which attracted insects and vermin.

Slowly the rug became a vital necessity for man; wherever he went, on his own back or on the back of his horse, buffalo, camel, or elephant, he carried his rug with him, so that he might always cover the ground on which he lay. On the backs of men, horses, buffaloes, camels, or elephants, the rug became a vital part of the baggage of the hunter and the primitive nomad. And when in crucial centuries—which the psychiatrist and philosopher Karl Jaspers called "Time-axes," designating thereby those periods in the evolution of nations when modern humanism and culture began to flower—Asiatic cultures invaded Europe, they brought with them on the backs of their horses the rare gift of rugs.

The rug thus attained a sovereign position among the domestic articles used by man. Originally the rug was used to cover cold damp floors; later it became a curtain over windows and walls or a hanging to conceal the entrance to a room. Used as tapestries, rugs were indeed a blessing to feudal lords, who bedecked themselves like playing-card kings and queens and drank from solid gold goblets, yet shivered with fever and chills caused by the dripping walls of their castles. The rug was pillow and mantle and even a mattress for people who had nothing else to sleep on. Piled one on top of the other, rugs were bed or sofa in the luxurious dwellings of Oriental satraps. When a man, rich or poor, died, the rug he used during his lifetime became his shroud or covered his coffin. Cut in strips, rugs lined the floors of long corridors, and cut in small foldable rectangles, they protected the knees of the believer when he said his prayers. Orientals used them as money, and in many countries they were the most precious gift that could be offered. The nomad hunter used the rug as his tent, and rugs covered the flanks of the restless mounts that bore the hordes of Genghis Khan over the Asiatic steppes. Folded and tied with cord, rugs were used as satchels by pilgrims. In palaces and churches, the rug as an ornament was often unsurpassed in sumptuousness. Along with jewels, silks, spices, and lovely female slaves, Oriental potentates offered gifts of priceless rugs woven by deft hands. Rolled up, the rug was used as a hiding place for fugitives and as a weapon to asphyxiate an enemy. Cleopatra, rolled up in a rug, gained access to Julius Caesar, and in the same fashion the last Caliph of Baghdad escaped from the besieged city. Multicolored rugs formed a polychrome frame for Scheherazade while she bewitched her Caliph for One Thousand and One Nights.

A history of mankind might be written by studying the evolution of rugs and the historical role they played in the drama of nations, just as Bachofen wrote a history of the ancient Greeks by studying the bas-reliefs on their tombs.

The rug is a powerful symbol of home. When an Arab street vendor rolls out a rug on the pavement he magically turns the spot into a home. That little square of many-hued fabric spread out on the sidewalk can counteract the subconscious fear also experienced by Western man when he passes from the security of his home to the insecurity of the street. It is as if the Arab had cut out a piece of the earth and transfigured it into a home, with the sky for a roof and the stars for lamps.

An object so intimately tied up with his life as the rug naturally impelled man to enhance its value by adding lovely ornamentation to its practical ends. Man embellished rugs with patterns and figures almost from the beginning, and onto these he projected those symbols of greatest importance to him, to his race, his country, or his times. As time passed, the rug became a magic cloth on which skillful fingers wove signs that imprisoned as in a magic cage the restless birds of symbols. To decipher the symbolism in Oriental rugs is to peer into a fabulous cryptographic world harboring the psychologic secrets of the peoples of the ancient Orient.

MAN'S CREATION AND ITS MEANING: ON AN AUTHOR AND HIS UNIQUE WORK

Surely there is nothing more important in life than understanding the meaning of one's work. At least once in his lifetime every man should ask himself two ques-

tions: What meaning is there to what I do? What does my work mean to me and to others?

Human labor may be classified into the practical and the theoretical. The first is related to man's immediate reality; it embraces all utilitarian and some scientific occupations. These occupations—mason, geologist, physician, carpenter, physicist, astronomer, farmer—refer to man's present and try to consolidate or improve it. The second group of noble occupations may focus on the past instead of the present. These are of a theoretical type and concentrate on tasks that at first sight may seem to be foreign to man's urgent needs. Among these are the research scientist, who is concerned with abstract questions (just as the physician is concerned with concrete questions), the historian, the sociologist, the mathematician, and the collector and preserver of rugs.

To be interested in rugs and to make of them one's lifework, one has to be a romantic. Only a man whose soul is open to the lyrical breezes of the universe can dedicate his existence to what is for so many simply an ornament or a utilitarian object. Every occupation is preceded by a *pre*occupation. Hence I was intrigued some time ago with *The Hidden Language of Oriental Rugs*,* by Harry Raphaelian, a man whose preoccupation and occupation have happily blended. For this book I had the pleasure of writing a short introduction on the subject of symbolism in modern psychology, and ever since then I have been interested in symbols on Oriental rugs.

Harry Raphaelian has lived almost half a century among rugs, collecting them, exchanging them, preserving them, studying them, and finally—this was the purpose of his unique book—glorifying them. Not satisfied with pointing out to the world the beauty of rugs, he imparted dignity to them by showing their psychologic value and their usefulness as instruments of historical research. He changed the rug from a merely decorative object to a scholarly book containing fragments of the soul of the peoples who wove the polychrome fabrics.

His book introduces us to a strange, dreamlike world. The horizon of Oriental history opens like a fan before us. The geographicohistorical belt whence came the loveliest Oriental rugs includes Turkey, Asia Minor, the Caucasus, Persia, the old Ottoman Empire, China, Turkestan, India, and Tibet. (It would be interesting to study why this "rug culture" concentrated around the waist of the planet. Such study would no doubt supply the key to the psychologic motivations behind the desire of these people to immortalize themselves in the art of rugs.)

The history of rugs has lent itself too much to the anecdotal and the adjectival and too little to the basically substantive.

It is possible to understand the gigantic leap from rustic rugs fashioned from Mesopotamian straw to the "Spring and Summer Rug," 84 square feet large, that decorated the Royal Palace of Ctesiphon in Khusraw near Baghdad. This rug, made of silk, gold, silver, and precious stones, symbolized might and power to the visitor, and ostentation and relaxation to the monarch. Not only its fabulous value—which today would be over 200 million dollars—but also its exquisite beauty inspired

* Anatol Sivas Publication, 1953, 230 pp.

Persian art in the centuries that followed. It is possible to understand the sharp contrast between the magnificence typical of Oriental rugs and the simplicity and sobriety of the sixteenth century Spanish woolen rugs from Alpujarras, and to understand why in periods of abundance and prosperity the opulent rug was preferred to the austere rug of lean years. But to this day no one has delved into the meaning of the symbols depicted in rugs. To descend into the rich mine of the symbolism of Oriental rugs and to bring the treasures of meaning out into the sun of our modern knowledge is the purpose of Harry Raphaelian's book.

To read through the pages of that book is to enter a palace with huge chambers representing the countries of the world, chambers reached through the long dark corridors of time. Fortunately, the author walks in front of us on this expedition through the night of centuries, opening windows and turning on lights. Under the spell of his word and the light of his torch, the figures on tapestries and rugs come to life, whisper to the reader, and open up a psychologic chest until now sealed. The author reveals by word and image—his word is simple and instructive, his image, brilliant and evocative—an exotic world palpitating with enigma and promise. He reveals the principal groups of symbols which century after century have preoccupied man. The author—born in Sivas, Anatolia, the fabulous land mentioned by Marco Polo in his *Travels*—presents enough material to write a history of the Orient based on the study of its textile symbols.

THE PSYCHOLOGIC ORIGIN OF SYMBOLS

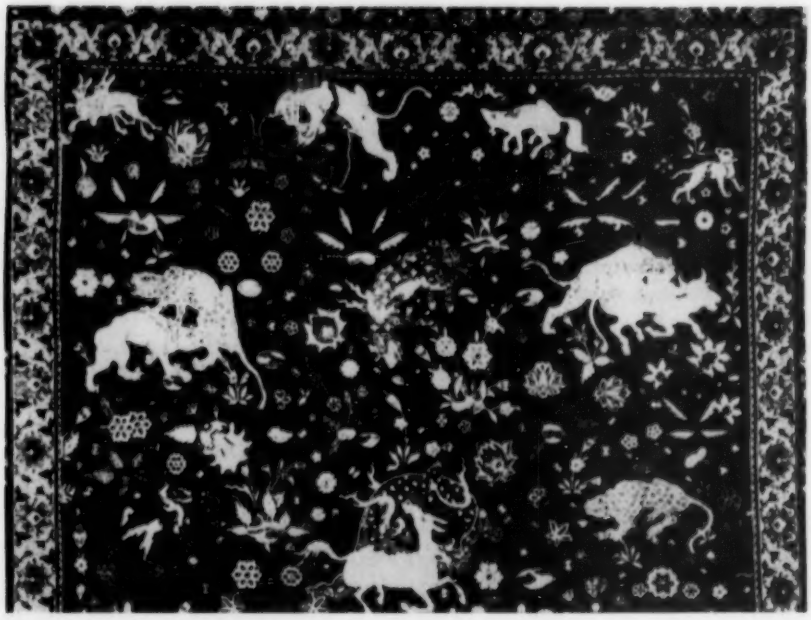
A symbol is not a rigid immutable entity, but something flexible that changes according to time and place, although preserving its basic emotional charge.

However important the individual analysis of a symbol may be, it is even more important to study it in correlation with other symbols and with the same symbol in other places and times.

Primitive man, who suffered from cosmic loneliness and confused the laws of his thought with those of Nature, created a means of communications and a technique to try to dominate demons and show his submission to the gods of the universe.

In his ignorance, primitive man ascribed the laws of Nature to superior beings—demons and gods. Fearful of these invisible powers, he devised means to fight them and to appease them. Thus man passed from the creation of myths to the rituals of magic. Especially impressed by the sun, the moon, and the stars, man's most primitive myths and symbols and even religions are of solar essence. The biography of every great Oriental religious reformer recounts the birth, apogee, and death of the prophet-god, apostle, or Messiah, that is to say, the dawn, high noon, and setting of the sun on its course from east to west. The sun is symbolized by the inner light and the mystic halo of the great religious reformers.

Everything related to the sun represents what is conscious and above the surface, and everything connected with the moon and stars represents what is submerged in the unconscious. The ancient symbols of tree, cross, and snake were at first identical with the symbol of the sun saving humanity after the Flood, since they represented the same images of death, salvation, and resurrection. The snake and the tree come to life in the spring and take on new skin and leaves, respectively. Paradise contained



Sixteenth century Persian Ispahan rug.

the tree of life, later symbolized by Christ on the cross; that is, the ideas of death and salvation, since the original sin was committed in the Garden of Eden. The deluge was meant to punish man, but the sun shone over the waters and saved him, just as Christ rose from the dead to save man.

With each myth there was born the magic rite capable of establishing ritual communication with gods and demons. That similarity of all primitive myths stems from the fact that their symbolism is born from the secret or latent experiences of man. One might draw up a map of primitive symbolism throughout the world, and its psychologic cartography would reveal that the conception of the world entertained by all peoples was identical.

With the passage of time, people forgot the meanings of their mystic symbols, but their individual associations of ideas and dreams still maintain their correspondence with the collective symbols and myths of mankind. That is why the study of symbols is so valuable to the psychiatrist and the historian. Through symbols we can delve into the deepest strata of the human soul, depths to which we would otherwise have no access.

An original if simplistic interpretation of some of the symbolic images observed in ancient art, especially in tapestries and rugs, is that offered by the anthropologist Edmund Dacque, who said that giants, hippogriffs, fairies, and fantastic animals really existed, and that primitive man was terrorized for thousands of years by the strange world about him. When those fabulous creatures disappeared, the psychic

trauma, the scar left on man's mind, was so deep that in order to liberate himself man created symbolic images—the dragon, the giant, witches—representative of those very same past terrors. If plumed serpents, winged bulls, hippogriffs and dragons, gnomes and fairies existed, the influence of alcohol or of a psychosis would be enough for modern man to establish contact again—in his delirium, hallucinations, or dreams—with those evil legions, which took refuge in his unconscious when they disappeared from the face of the earth.

But this fantastic photographic interpretation by Dacque of primitive symbolism cannot compare with the study of symbolism as it stemmed from primitive magic and religions, in which men wished to dominate demoniac powers through magic rituals or invocation, or to submit to beneficent deities through religious rituals and the cajoling influence of prayer. Magic was a way of conquering; prayer was a way of submitting. Magic was aggressive; religion was defensive.

Gradually man created religions of fertility to overcome his fear of loneliness and religions of mystery to overcome his fear of death. Thus he abandoned his earlier worship of demons. The fertility religions overcame loneliness by glorifying the idea of reproduction as symbolized by harvest festivals and the worship of Mother Earth. The mystery religions provided spiritual refuge for man desiring to attain immortality, and produced the rituals celebrated in the Eleusinian temples.

THE PSYCHOLOGY OF ANIMALS THAT NEVER WERE

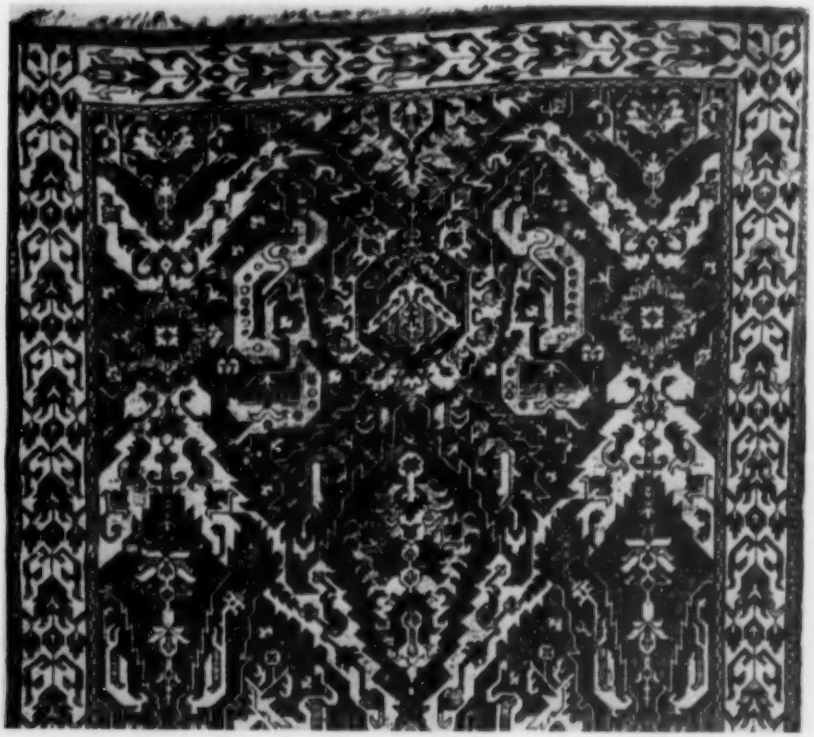
Later, magic evolved and became the individual ritual of the neurotic, while religion changed into collective neurosis. But there still remained some of the individual fears, and these were projected as animal symbols.

The bird became a phallic symbol, just as the peacock became the symbol of death. The horse, which found its maximum symbolic expression in the Greek centaur—as savage as Eurythion or as beneficent as Chiron—was the archetype of sexual power. It originated in Thessaly, where the idea of the hunter of bulls who loved his horse and the idea of the horse itself were fused into one symbol. Bulls, goats, and insects symbolized the primitive passions in Egyptian mythology. In the cult of Ishtar, Siva rode on a bull and symbolized death; Imdra rode an elephant and symbolized rain and thunder. The fish was the symbol of the Saviour (his Greek name was an acrostic of the words designating "Jesus Christ Son of the God Saviour"); the boat was the symbol of the Church on the sea of life. The lion also was the symbol of Christ, "Lion of the tribe of Judah" (Revelation 5).

These fabulous animals, which never existed except in peoples' imaginations, make up one of the most interesting groups of symbols in Oriental rugs. Many of these animals belong to the beginning of mankind, and in many instances were created in an attempt to explain the inexplicable in the universe. Later, the Assyrian priests, who from the peak of lofty hills scrutinized the stars, projected into the heavenly constellations the figures of the animals—goats, fishes, scorpions—that inhabited their fancies.

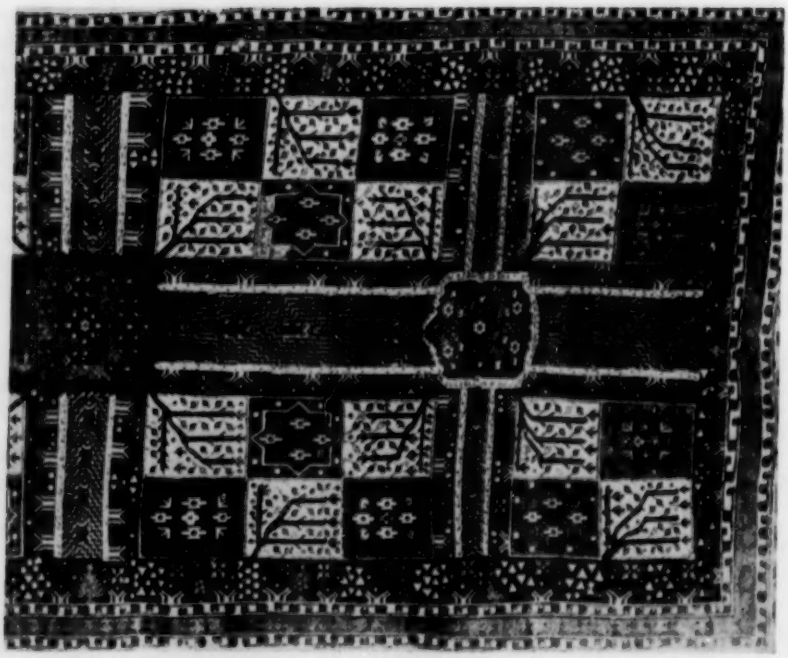
Fantastic animals do not appear only on rugs. Greek plates of the Corinthian period (600 B.C.) show terrible creatures with three heads—in front they are lions, in back, serpents, and in the middle, goats. These were the enemies against which

Greek heroes pitted their strength. We have already mentioned the centaur, half man, half horse, which six centuries before Christ symbolized for the Greeks the savage aspect of man. Two thousand years before Christ there existed sphinxes—the ancient Egyptian symbol of royal power—with a human head, usually resembling some Pharaoh, and with the body of a lion to indicate the strength of royalty. When they reached Greece almost fifteen centuries later, these sphinxes were no longer royal symbols. Winged horses, which nine centuries before our era stood watch over the doors of the ancient Assyrian palaces to prevent the entrance of evil spirits, gave rise to Pegasus, the winged horse that the Greek hero Bellerophon broke in with a magic bridle. These effigies were immortalized in the Greek vases of Campania in the fourteenth century A.D., and later in the winged lion of Venice, the



Eastern Caucasus Dragon Carpet, Kuba Region, end of sixteenth century. Flanking the medial line are highly conventionalized dragons, khilins, and phoenix fighting. The serrated bands dividing the field are decorated with ducks, phoenix, and heavy blossoms.

The carpet displays austerity, seizing power, robust color, forceful silhouettes. The vast grandeur and savage contours of the Caucasus Mountains seem to be transmuted directly into the design. The patterns display a violent and ingenious unexpectedness, the product not of a tame or civilized fancy, but rather of some powerful foreign world.



Northwest Persia Garden Carpet, eighteenth century. In the center is a canal indicated by zigzag blue lines on a deep crimson ground with side canals of similar pattern. The rest of the field is divided into squares containing conventionalized flowers and trees in rose, ivory, green, and light blue. These beds are surrounded by similar floral devices. The border consists of a strong reciprocal between two white guard strips with blocklike leaves on straight stems.

It is generally thought that patterns such as these represent a continuation of the famous Spring and Summer Rug of Khusraw. The garden, in Persian life, was a source of joy and comfort in a land of brilliant light, frequent heat, and much aridity—it has always been a symbol for Paradise. The carpet shows the usual plan of Persian gardens even today—formal beds divided by water courses.

symbol of Saint Mark, patron saint of that romantic city. In the Middle Ages the hippogriff appeared in church architecture with the head and wings of an eagle, to indicate the power of the Church in heaven, and a lion's body, to denote its strength on earth. Fantastic birds like the Chinese fêng-huang, which appeared only in times of peace and prosperity, still seem to beat their wings on the polychrome woodcuts of the Ming dynasty. Another fabulous animal was the chi-lin of Chinese bronzes. It has a stag's body, horse's hooves, and the tail of an ox, and it treads delicately to avoid crushing the grass and insects. In Japan, this animal was called lirin, and alongside it were placed sea serpents, hydras, griffins, and especially unicorns and dragons.

The unicorn was a graceful beast with the body of a horse, the hooves of a stag, the tail of a lion, and a single horn protruding from its forehead like a petrified

sprout. During the Middle Ages, it was the symbol of purity and tenderness. Bronze unicorns pouring forth holy water may still be seen in old churches. Flemish tapestries of the fifteenth century depicted the hunt with hounds of the unicorn, "that austere and noble animal" of blond mane, but only the pure hands of a virgin could overcome it. Later, medieval folklore changed the unicorn into the symbol of Christ, the virgin-huntress became an emblem of the Virgin Mary, while the chase became the allegory of Christ's passion. The legend of the unicorn, mentioned as far back as Pliny, was born in the Orient, where it was considered the spirit of the earth, just as the dragon was the spirit of the air and the phoenix the spirit of fire. The pointed polished horn of the unicorn was a universal panacea. Only four centuries ago it still brought a high price in Dresden, although it was probably only a piece of ivory endowed with curative powers by the faith of the times. The power of the unicorn's horn against poisons derived from its being the symbol of Christianity, the emblem of mystical purity, capable of disintoxicating souls and specific poisons. At the same time, its prolific magic powers (it was the symbol of the Earth, the Mother of all living things) conciliated the attributes of virginity and fertility.

Even before the unicorn, the dragon, another favorite symbol in Oriental rugs, appeared in folklore. Of this, G. K. Chesterton said, "The dragon is certainly the most cosmopolitan of all impossibilities." Many years later, still fascinated by fantastic animals, Chesterton, out in the country, drew with colored chalk the soul of a cow: ". . . *and the soul was all purple and silver and had seven horns and the mystery which all beasts carry in them.*"

In China, dragons were considered friendly animals; in other places, they were symbols of Satan. Some inhabited the sky and ruled the winds and the rain. In all mythologies the flying dragon, the earth-dragon, and the fire-dragon were the basic elements of myths, fables, and legends. Today, in children's fancies as well as in the nightmares of adults and the deliriums of psychotics, the dragon still is the symbol of man's greatest fears. In weaving dragons into rugs, man perhaps tried to come to terms with them by offering them artistic tribute as well as shelter in his home, and perhaps subconsciously he also allowed himself the pleasure of stepping on the effigy of the much feared animal.

Primitive animism and Oriental rugs are full of these theriomorphic symbols, which can be explained psychologically by the fact that man at once loved, hated, and feared the animals with which he lived, and in order to express his emotional ambivalence with regard to these animals, he projected into symbols this complex of contradictory emotions.

THE SYMBOLISM IN RUGS—BASIS FOR A NEW PSYCHOLOGIC HISTORY OF MAN

Behind every symbol there is a real fact disguised or hidden. Symbols are closely allied to myths, and it is well known that myths are born historically at moments of national peril, when the imagination of men is fired. Excavations in Crete, Mycenae, and Troy have revealed that Greek myths symbolized the struggles that

took place 3000 years ago between the old Minoan civilization of the South and the invaders from the North. The myths, such as the minotaur, adorning many Oriental rugs in the form of symbols were developed in a similar manner. The bull was Crete's national symbol, and the palace of Cnossus—in which the image of the bull was everywhere—was its labyrinth. The Athenians represented the bull symbolically as a cruel monster which every seven years demanded a tribute of fine young men and beautiful maidens. In truth, the bull was the symbolic projection of the fact that for many years the Cretans demanded tribute from the Athenians. The myth of the Argonauts represented symbolically the effort of the invaders from the North to colonize the area up to the Black Sea, after the destruction of the Mycenaean civilization of Troy.

Dreams today are the myths of the individual, just as myths were the dreams of peoples. The human being is essentially a creator of images. Most animals proceed by instinct, and action follows perception automatically. But in man, perception is not immediately transformed into reaction. With man some time intervenes during which selection is made, and at such time our images, ideas, and symbols take shape. Our frustrated desires, our unfulfilled dreams, what we love and what we hate, everything that is of importance in our mind we project in the form of symbols that eventually find their way into works of art and decorative objects, especially objects that play, as rugs do, an important part in the history of mankind.

By integrating the symbols, one could explain why the favorite motif on Persian rugs is the garden; why birds, peacocks, human figures, and bright colors are omnipresent on Turkish rugs; why the Tartars loved browns and purples; why the Chinese preferred blues and yellows, the Persians, red-browns and dark blues. One could correlate these symbols with historical periods and trace the geographic profile of each country, and interpret them not only in the light of the psychology of a specific nation and its time, but in relation to similar symbols at other times, keeping in mind the different meanings of the same symbols in different countries. The result would be a history of nations in the light of their symbols, a history in which the rug would play a unique role in revealing the deepest strata of the popular soul.

After all, the fingers that wove every rug were propelled by a brain bathed by the historicultural currents of a given period and a specific country. The symbol that the artisan's hands wove into the rug was the projection not only of his subconscious motives, but also of those of his people and of his time. The rug thus became a blackboard on which a people wrote its secret dream life in the cabalistic language of symbols.

If all the rugs produced by any one country throughout its entire history were put together, they would make up the multicolored pages of a fabulous book containing the unwritten story of its fears, loves, hates, ideals, frustrations, and ambitions. All together the rugs produced in the entire world at a given period would, like magic stained-glass windows, reveal the differences and affinities between their symbols, and would trace a polychrome map of the human unconscious as projected on the screen of History.

NEW ANTIBIOTICS TO BE ANNOUNCED. 156 papers by leading investigators will be presented at the Fourth Annual Symposium on Antibiotics, sponsored by the Division of Antibiotics, U. S. Dept. of Health, Education, and Welfare, in collaboration with the journals, Antibiotics & Chemotherapy and Antibiotic Medicine & Clinical Therapy, on October 17, 18, and 19, 1956, at the Willard Hotel in Washington, D. C. Also, Panel Discussions on the following topics will take place: "Antibiotics in Intestinal Antisepsis," "Susceptibility of Microorganisms to Antibiotics Isolated From Hospitalized and Nonhospitalized Persons," and "Present Status of Antibiotics in the Preservation of Food." Besides papers announcing new antibiotics, there will be other studies on laboratory research work, clinical application of antibiotics, and the use of antibiotics in food preservation. All those interested are invited to attend this meeting.

RESEARCH AWARDS. Applications by research investigators for support of studies in or related to the cardiovascular field are now being accepted by the American Heart Association. The awards would be for the fiscal year beginning July 1, 1957. Further information is available from the Medical Director, American Heart Association, 44 East 23rd Street, New York City 10.

BARBITURATE POISONING THERAPY. Hemodialysis has been found to be an effective treatment for acute intoxication by barbiturates such as phenobarbital and pentobarbital. Twenty-six patients were studied, 8 of whom were treated with a Kolff hemodialyzer. The higher the initial concentration of barbiturate in the blood, the greater was the rate of removal, the efficiency of the hemodialysis improving as the patient's clinical condition improved.[1]

ARTERIAL VASODILATOR. A new drug called azapetine (Ilidar) has been found effective in the treatment of patients with peripheral vascular diseases by relieving spasm and blocking arteries. Azapetine can be administered orally or intravenously.[2]

PEDIATRIC ALLERGY. A postgraduate course in pediatric allergy will be held at the New York Medical College, Flower and Fifth Avenue Hospitals, under the direction of Bret

Ratner, Professor of Clinical Pediatrics and Associate Professor of Immunology, Nov. 7, 1956, to May 29, 1957 (30 sessions), on Wednesdays, 9 A.M. to 4 P.M. Further information may be obtained from the Office of the Dean, New York Medical College, Fifth Avenue at 106th Street, New York City 29. A research fellowship in pediatric allergy is also available. Application should be made immediately.

NEW HEART STETHOSCOPE. At Philadelphia General Hospital a new stethoscope has been introduced that is inserted directly into the heart. It consists of a tiny barium titanate crystal mounted on the tip of a heart catheter. The crystal converts the heart sounds into electric pulsations, which are then reconverted into sound.

WORLD MEDICAL ASSOCIATION MEETS. The opening plenary session of the Tenth General Assembly of the World Medical Association will convene in Havana on Oct. 10, 1956, Cuban Independence Day. Sessions will continue through Oct. 14.

USE OF RADIOISOTOPES. The special training division of the Oak Ridge Institute of Nuclear Studies is offering a four week course in the techniques of using radioisotopes beginning on Oct. 22, 1956, on Jan. 7, 1957, and on Feb. 4, 1957. For information, contact the Special Training Division, Oak Ridge Institute of Nuclear Studies, P.O. Box 117, Oak Ridge, Tenn.

PUBLIC HEALTH ASSOCIATION MEETING. Progress in preventing health hazards and diseases, ranging from highway accidents to the common cold, will be reviewed by more than 4000 public health specialists in 81 sessions at the 84th annual meeting of the American Public Health Association and meetings of 40 related organizations in the Atlantic City Convention Hall, November 12 to 16. Further information may be obtained from Reginald M. Atwater, M.D., executive secretary, American Public Health Association, 1790 Broadway, New York City 19.

DERMATOLOGICAL ASSOCIATION AWARDS. The American Dermatological Association is offering a series of awards for the best essays submitted for original work, not previously published, relating to some fundamental aspect of dermatology or syphilology. The cash awards will range from $500 to $200. For information write to J. Lamar Callaway, secretary, American Dermatological Association, Duke Hospital, Durham, N. C.

BIBLIOGRAPHY

1. Berman, L. B.; Jones, H. J.; Schreiner, G. E., and Pallotta, A. J.: J. A. M. A. 161:820 (June 30) 1956.
2. Stallworth, J. M., and Jeffories, J. V.: J. A. M. A. 161:840 (June 30) 1956.

Genesis of Cancer

It is the merit of present-day science that the old divisions between physics, chemistry, biology, and medicine have largely disappeared. In the realm of living organisms, the hyphenated scientist is the man at the helm, as in bio-physics, bio-chemistry, bio-electricity, et al.

The latest synthesis of several sciences is in the theory of Professor Otto Warburg, Nobel laureate and distinguished director of the Max Planck Institute for Cell Physiology, that the genesis of all cancerous growth lies in a disturbance of a cell's energy supply. Briefly, the main points in the theory[1] are that cells obtain their energy through either respiration or fermentation. When respiratory mechanisms in a cell are severely damaged, through a variety of mechanical or chemical means, the cell is obliged to resort to fermentation to remain alive. It manages to do this but only at the cost of losing some of its power of differentiation. In time, damaged cells continue to live and multiply, but only as a mass of shapeless undifferentiated tissue, commonly called a cancerous growth.

That cancerous processes originate in some irreversible biologic change in a cell, caused by an exogenous or endogenous "stress" in the cell's normal metabolism, is a thesis now widely accepted, although the viral origin of cancer still has many distinguished proponents. The stress may be mechanical irritation, as in the case of lungs exposed to injurious aerosols. It can be chemical, as shown in the high incidence of lung cancer among persons exposed to hydrocarbon or arsenical fumes.* And, of course, the relationship between various forms of radiation and cancerous growth is fairly solidly established.

More recently, Satterlee[2] lent support to the Warburgian choice of arsenical compounds as carcinogenic factors by a study of arsenic in tobacco products and polluted city air. A disturbing revelation is that the arsenic content of American tobacco cigarettes increased in 20 years from an average of 12.6 μg./cigarette in 1932 to 42 μg. in 1950–1951, or more than 300 per cent; during that time cigarette consumption in the United States rose also by 300 per cent. Satterlee compares the rise in the arsenic content of cigarettes with an increase in the death rate from lung cancer in males by 600 per cent during the period under review. We have long been suspicious of correlated statistics of this nature, but the facts must be set down nevertheless.

The arsenic in tobacco (not confined to cigarettes) comes from many years of using arsenical compounds as pesticides in the tobacco-growing areas. Although these were banned in 1946, and organic pesticides substituted, the soil of tobacco plantations continues to hold residues of arsenate of lead, which release arsenic in soluble form to be absorbed by tobacco plant roots. Similarly, the expansion of industrial and chemical manufacture has pumped increased quantities of arsenical compounds

* Professor Warburg's thesis selects arsenious acid as a basic example of a "strong specific respiratory poison."

into the atmosphere. Further investigation of these two elements in carcinogenesis, as Satterlee emphasizes, is urgently needed.

Taking a broader view of the problem of carcinogenesis, it is quite understandable that any form of injury to a cell must be a severe challenge to that primitive organism's will to survive. As the French saying has it: *cet animal n'est pas méchant, quand on l'attaque, il se défend.* If certain mitochondria in a cell are injured, the cell is entirely justified in attempting to survive with what equipment is left to it.

One question in the Warburgian theory is whether in fact damage to mitochondria in one cell is genetically transmitted to the mitochondria of the daughter cells, in other words, how far an irreversible process can become hereditary. Another question is whether the observed differences between respiration and fermentation in lower forms of life, such as yeast cells, can be correlated with the cell life of warm-blooded animals. Answers to such questions will require many more difficult experimental procedures before they become definitive. It should be noted in passing that Professor Warburg has launched several other startling theories in the past which, in time, were proved to be experimental fact.

For the practicing physician, these theories and studies may prove to be a shade too academic, insofar as relations with patients are concerned. It is no consolation to relatives of cancer-stricken patients to be told that the malignant growth may be the result of arsenic inhaled 30 years previously. The variety of insults that may, according to the Warburgian theory, cause irreversible and hereditary damage to a cell is enormous. To protect himself from them all, a human being would have to become a cocoon, sedulously sheltered from all the "slings and arrows" of modern life.

Whatever the physicochemical origin of cancerous growths may be, it is heartening that so many skilled researchers and clinicians are still concentrating on the therapy of cancer. The Warburgian theory, if it is proved correct, may satisfy man's eternal curiosity about life and death; it will still be left to the physician's devotion and skill to prolong life and cheat death.

BIBLIOGRAPHY

1. Warburg, O.: On the origin of cancer cells, Science *123*:309 (Feb. 24) 1956.
2. Satterlee, H. S.: The problem of arsenic in American cigarette tobacco, New England J. Med. *254*:1149 (June 21) 1956.

GENERAL PRACTICE CLINICS

This section of General Practice Clinics features reports on papers delivered at current medical meetings in the United States and abroad.

Intensive Recreational Activity in Treatment of Schizophrenic Patients

Presented by MARTIN W. MEYER, ED. D., before the American Association for Health, Physical Education and Recreation, Chicago, Ill., March 24–30, 1956.

Three hours of intensive recreational activities five days a week over a period of six months had significantly improved the behavior of long-term chronic schizophrenic patients at the Montrose, New York, Veterans Administration Hospital. The patients had been hospitalized from 3 to 28 years and they ranged in age from 29 to 62 years. They were selected from a group of 202 idlers and sitters among the hospital population and were matched in sets of 3, according to age, length of stay in the hospital, and rating on the Montrose behavior rating scale. One group of 20 patients participated in activities like those they engaged in prior to illness, a second group participated in activities new to their experience, while a third group was used as controls in the study. After three months of recreational activity, the group engaging in premorbid learned activities was significantly better than the second group, but after six months, the difference was no longer significant. A follow-up study is now being made combining recreation and occupational therapy.

Clinical Aspects of Collagen Diseases

Presented by RAYMOND W. BRUST (Philadelphia General Hospital) before the Philadelphia General Hospital Medical Division, Philadelphia, Pa., March 15, 1956.

Collagen diseases include lupus erythematosus, rheumatoid arthritis, rheumatic fever, scleroderma, dermatomyositis, thrombotic thrombocytopenia, African collagenosis, and possibly several other rarer diseases. The pathology consists of alteration of the collagen fibers of the connective tissue. Signs and symptoms of these diseases have certain things in common. There are obscure, vague symptoms occurring in many parts of the body, frequently affecting the serous cavities. Microscopic or gross hematuria may be present. Fever, headache, malaise, weakness, pulmonary signs, such as shortness of breath, and gastrointestinal signs, such as anorexia, are found. There seems to be both progression of the disease and recovery superimposed on each other, causing these various signs and symptoms.

Acute lupus erythematosus is usually found in young adult white women but has been found by us in Negro women also and in white and Negro men. Symptoms are malaise, arthralgia, pleuritis, skin eruption, and edema. The butterfly lesion across the nose is not always seen. Cardiovascular phenomena include a friction rub, arrhythmias, and Raynaud's phenomenon, and occasionally the picture is typical of subacute bacterial endocarditis of the atypical verrucous or Libman-Sacks nature. All sorts of skin lesions may be found. The laboratory tests show red blood cells and casts in the urine. Leukopenia from 2000 to 5000 white blood cells/cu. mm. is frequently found, with mild anemia, an increased sedimentation rate, an increased serum protein with a reversed albumin-globulin ratio, and lupus erythematosus cells in the bone marrow. These cells are leukocytes that have phagocytized the products of the breakdown of the diseased nuclei of other leukocytes.

Polyarteritis is found in the medium-sized veins and arteries, usually in the medial coat. The symptoms are extremely varied because any artery or vein may be involved. The patient's age usually ranges from 20 to 40 years, although polyarteritis has been recorded from the age of 10 days to 77 years. There are six main signs: leukocytosis, eosinophilia, albuminuria with casts and red blood cells, abdominal pain, hypertension, and purpura with nodules. This is believed to be an allergic disease because of the eosinophilia, and it can be experimentally produced in laboratory animals by means of a sensitivity reaction. Diagnosis is difficult because of the extreme number of symptoms, which are frequently due to evidences of healing and progressive disease occurring at the same time. Definitive diagnosis is by skin or muscle biopsy and the finding of typical pathologic lesions.

Scleroderma may be of two types, focal or diffuse. Acrosclerosis is associated with Raynaud's phenomenon. Later in the disease, visceral involvement occurs. The focal type is usually benign. In the diffuse type the skin becomes tight, the facies are drawn into a mask by this tightness, and there are paresthesias and decreased sensation. Dyspnea occurs from lung and heart involvement. Universal calcification is found in this disease (the Thibierge-Weissenbach syndrome) more than in other collagen diseases. The early case may be characterized only by Raynaud's phenomenon with other vague symptoms.

The onset of dermatomyositis usually follows an upper respiratory tract infection. It shows arthralgia, purpura, and dysphagia. Scleroderma may be associated. The skeletal muscles are chiefly involved, but eventually the cardiac muscle becomes involved, leading to death. There is a 50 per cent mortality. Muscle contractures and weakness lead to progressive weakness. Early diagnosis is made by biopsy of muscle and by blood smears. The triad of edema, a skin rash, and muscle changes is diagnostic.

Thrombotic thrombocytopenia basically is a vascular lesion with the subintimal area being involved rather than the media. In the acute stages, thrombocytopenic purpura is found with hemolytic anemia. Changing neurologic signs occur. The subacute stage shows a slower onset of the same signs. Both of these types are fatal. The age of onset ranges from 6 to 69 years and may be associated with other collagen diseases. Symptoms include chilliness due to the anemia, weight loss, abdominal pain, cutaneous lesions due to the purpura, epistaxis, and, most important, neurologic

signs of any kind. There are few cardiac symptoms. Pallor is present. The liver and spleen are enlarged, and there may be jaundice. Laboratory tests show a positive Rumpel-Leede test; the direct Coombs test is negative. Retinal changes may be found, such as hemorrhage and exudates. Diagnosis is made in the presence of a normocytic anemia with an increased sedimentation rate and neurologic signs. The lupus erythematosus test is negative. A false positive serologic test for syphilis may occur with this disease. It is usually fatal in six months.

Mode of Action of the Mercurial Diuretics

Presented by ROBERT F. PITTS (Cornell University School of Medicine, New York, N. Y.) before the Boston City Hospital House Officers' Association, Boston City Hospital, March 14, 1956.

All the organic mercurial diuretics in common use are compounds with a terminal mercury linkage and a 2-methoxy group. They are administered as their thioglycolate or theophylline derivative. These derivatives reduce local pain, reduce cardiotoxicity, and speed absorption. For the first 10 years after their clinical introduction, it was believed that mercurial diuretics work by mobilizing peripheral tissue fluid. It was not until Bartram's classic experiment that it was appreciated that the site of action is in the kidney. This experiment proved three points: mercurial diuretics act directly on the kidney; they are fixed in renal tissue and have a prolonged effect; and in high dosage, they can cause renal damage and renal shutdown. The mercurial diuretics exert their action by blocking a limited fraction of reabsorption of salt by the kidney tubules. When a normal dose of a mercurial diuretic is injected, sodium excretion and urine flow increase promptly, and sodium and chloride reabsorption is decreased to about 83 per cent of normal at the peak of the diuresis. The significant factor is the blocking of the reabsorption of sodium and chloride. Brodsky demonstrated that diuresis is produced by the excretion of ions that pull water with them. The greater the excretion of ions, the greater the excretion of water.

The minimal toxic dose of mercury produces lesions of the distal third of the proximal convoluted tubules. Larger doses damage the entire kidney tubule. Mercury is concentrated in the kidney cortex in far greater concentration than in any other tissue. Using radioactive mercury, the concentration with a normal diuresing dose of a tagged organic mercurial diuretic in the renal cortex of dogs was found to be slightly less than 10^{-4} moles. Mercury in these concentrations is known to block sulfhydryl groups of certain enzymes. During the height of diuresis in dogs, plugs were cut from the kidney and measured for radioactivity, using mercury-tagged chlormerodrin. The maximum concentration was found in the cortex; it decreased rapidly in the medulla, and there was practically no activity in the papilla. In the final analysis, it is still unknown what enzyme systems are affected or in which portion of the tubules the diuretics act.

According to Müller, chlormerodrin, as well as the other mercurial diuretics, is excreted rapidly in the urine, in combination with either cysteine or acetyl-cysteine. The diuretics are eliminated by tubular excretion. Mercury clearance reaches a

maximum at the peak of diuresis. This clearance is approximately one-half the filtration rate. When 2,3-dimercaptopropanol (BAL) is given, the renal clearance jumps to about three times the filtration rate, and the diuresis promptly stops. BAL liberates the mercurial from its combination in the renal tubule, and it is excreted in the urine. When mercurial diuretics are injected intravenously, almost 50 per cent of the diuretic may be removed from the plasma by the lungs in the first circulation of the blood through that tissue. It is later fed back into the blood to be fixed in large part in the kidney cortex.

New Antibiotic Concepts

Presented by MAXWELL FINLAND (Harvard University School of Medicine) before the Cambridge City Hospital, Cambridge, Mass., March 15, 1956.

It is best to refer to the group of agents that work directly on bacteria and not on the individual's defense- or antibody-producing mechanisms as antimicrobial rather than antibiotic drugs. There are two groups of antimicrobial agents: chemical agents, which are synthesized chemicals, and antibiotics, which are, at least in the first instance, made by higher bacteria or molds. Sulfa drugs were not the first but the most important group of antimicrobial drugs. Next came penicillin, which handled infection more readily than the sulfonamides and almost completely replaced them, except in special circumstances, such as urinary tract infections.

Meningococci and gonococci, both gram-negative, were first successfully managed with sulfonamides. Then the gonococci began to respond less readily to these compounds. On the other hand, meningococci remained very highly susceptible to any sulfonamide drug, especially sulfadiazine. This is one case where sulfonamide drugs were more effective than penicillin. But still, meningococci are highly susceptible to penicillin; penicillin does not easily penetrate the cerebrospinal barrier, and large doses must be used to treat meningococcal meningitis. However, as little as 0.5 Gm. of sulfonamide may be adequate to cure the carrier state and even some infections, although the usual doses are given in treatment of active infections. In this case, sulfonamides are the drugs of choice. Except for this infection, and perhaps bacillary dysentery, antibiotics are better for all infections. During the Korean war, bacillary dysentery, caused by certain strains of Flexner's bacillus, was found to be best treated with the tetracycline drugs.

There is one objection to treating streptococcal infections with sulfonamide drugs, which is sometimes done today, namely, that they do not get rid of all the streptococci. Therefore, persons treated with sulfonamides can subsequently spread the streptococci to others or reinfect themselves. Treating a streptococcal infection with penicillin for 7 to 10 days will usually kill all the organisms. Also, early treatment with penicillin will prevent septic as well as nonseptic complications, such as rheumatic fever and glomerulonephritis. The type of urinary tract infection that can improve can be successfully treated with tetracycline, nitrofurantoin, mandelic acid, and sulfonamides. The other types are resistant to all forms of treatment and are usually associated with some mechanical obstruction in the tract that prevents the

drug from getting to the organisms, or is caused by organisms that are resistant to all the agents.

The question is frequently raised of whether or not the sulfonamide drugs should be used prophylactically. During World War II, they were found to be generally effective in preventing streptococcal infections. Then some strains that were resistant appeared and produced serious epidemics. Streptococci types 17 and 19 were most commonly involved. These strains are not frequently found in the general population; so there is still some value in using the sulfonamides for the prophylaxis of rheumatic fever or streptococcal infections. The only disadvantage in the continuous use of the sulfonamide drugs is that in some persons they may cause bone marrow depression. Frequently, doctors use the sulfonamide drugs to treat urinary tract infections, once they have been controlled with a broad-spectrum antibiotic. Once a broad-spectrum antibiotic is used, however, it is probably best to continue using that drug to keep the infection in control.

Penicillin was the first antibiotic and is still the best, although it has a limited spectrum of activity. It is the best drug for all coccal infections. It has its widest activity against gram-positive organisms. Clostridia infections are best treated with penicillin, but high doses are required. Penicillin is the drug of choice for treating *Streptococcus viridans* infection; it has the advantage that large doses can be used, even as much as 100,000,000 units/day. No other drug can be used with such a wide dosage range so safely. Penicillin is still effective in treating staphylococcal infections caused by susceptible strains, but they require higher doses of penicillin than other coccal infections and it must be used for long periods. Next to the gonococci, the group A hemolytic streptococci and the pneumococci are the most susceptible to penicillin.

Penicillin is washed out very rapidly into the urine. With injectable penicillin, there is a rapid high peak of concentration of the drug in the plasma. Procaine was found to form a salt with penicillin that was insoluble and, when injected, would release penicillin slowly. Orally, penicillin G is inactivated by acidity of the stomach, about four fifths of the activity being lost as it passes through the stomach. Using buffered tablets and giving the preparation before meals when the acidity is lowest were found to decrease the amount of acid inactivation. Recently, a penicillin with an extra methyl and oxygen molecule has been found that is acid-resistant. This is penicillin V. It is about twice as effective orally as penicillin G, but is destroyed faster when injected and therefore finds its advantage only in oral preparations. Dibenzylethylenediamine dipenicillin G, a benzathine penicillin, has a much longer action than other penicillins when injected intramuscularly. Its activity lasts seven days to one month. In prophylactic use, where only small doses are needed, one injection of 600,000 to 1,200,000 units/month is adequate. The disadvantage of this is that it causes local tissue damage and may cause a higher rate of sensitization to penicillin. However, to date there is no evidence that increased sensitivity is a serious drawback. The main toxic effect of penicillin is its sensitization, which manifests itself particularly in the form of rashes and occurs most frequently in persons with an allergic history. In cases of rashes where penicillin is the drug of choice, the allergic response can often be controlled by the use of anti-

histamines or cortisone. Deaths have resulted mostly from parenteral injections of repository preparation, particularly procaine penicillin.

Streptomycin was the next major antibiotic, its main activity being against the tubercle bacillus and gram-negative organisms. Streptomycin is more effective in an alkaline medium. If the urine can be made more alkaline, streptomycin is 20 to 40 times more effective than penicillin in treating genitourinary infections, and its resistance rates are also lower. The treatment of tuberculosis became the major use of the drug, but the disadvantage of streptomycin was that resistant organisms developed, especially in the focal type, because the drug does not penetrate these infections well. Then para-aminosalicylic acid (PAS) was found to enhance the effect of streptomycin and decrease the rate of development of resistant strains. Giving PAS with streptomycin revolutionized the treatment of tuberculosis and decreased the amount of streptomycin needed so that eighth nerve damage was no longer a problem. Next came isonicotinyl hydrazide (INH), which again revolutionized the treatment of tuberculosis. With INH, resistance developed rapidly, but when given with PAS, this was again decreased. INH and PAS given orally are the best combination at present, and streptomycin is needed only in severe cases, especially miliary and meningeal forms.

The next drugs were the broad-spectrum antibiotics, including chloramphenicol and the tetracyclines. These are all effective against a wide spectrum of bacteria and some large viruses. They are all effective against rickettsia, psittacosis, atypical pneumonia, to a certain extent, and lymphogranuloma venereum. Rickettsial diseases such as Rocky Mountain spotted fever, murine typhus, and Q fever are effectively treated by the broad-spectrum antibiotics. The tetracyclines have a slightly greater effectiveness against the gram-positive organisms, while the gram-negative organisms are slightly more sensitive to chloramphenicol.

Erythromycin is primarily effective against gram-positive bacteria. At first, it attacked all strains of staphylococci against which it was tested. Now, about 15 per cent of staphylococcal infections in most hospitals are resistant. Using certain combinations, such as erythromycin with chloramphenicol, reduces the number of resistant strains that may emerge during antibiotic treatment. The best combination varies in different hospitals. The tetracyclines produce gastrointestinal disturbances, but rarely rashes. Chloramphenicol also rarely produces rashes but may occasionally produce serious bone marrow depression. Combinations of various antibiotics are often helpful, but occasionally are harmful. Antagonism can be readily shown in the test tube, but infrequently in man.

Sigmoidoscopy in General Practice

Presented by KENNETH C. HUTCHIN, M.D. (Hatfield Herts, England) before the Royal Society of Medicine, General Practice Section, London, England, March 21, 1956.

The use of sigmoidoscopy in general practice must be extremely rare; even in consulting practice it is not often used, except by proctologists. Its value is that it can be employed to diagnose diseases of the lower bowel long before disease can be de-

tected radiologically. Direct vision, with biopsy if necessary, is the best method of diagnosis. Cancer of the lower bowel can be diagnosed with the sigmoidoscope before symptoms are present. The only preparation required before sigmoidoscopy is that the patient should defecate. Washouts and purges alter the appearance of the mucous membrane, and, if used, should be given a few days before the examination. A bowel washout may actually remove pathologic material of diagnostic significance, e.g., mucus or blood, and it may produce an inflamed and reddened mucous membrane.

It is advisable for the patient's comfort not to inflate the bowel during the passage of the sigmoidoscope. The position of the patient is important. The true knee-chest position should be assumed, with the chest flat on the bed and the spine arched downward. Then the sigmoidoscope is passed forward and slightly downward. Once the internal sphincter is passed, the obturator is removed and the light switched on. The battery from an ophthalmoscope may be used as a source of light. The passage of the instrument is now controlled by direct vision, and it is advanced only along the lumen of the bowel where this can be actually seen. No force is applied, but the weight of the instrument is used to advance it along the bowel.

The normal mucous membrane is light pink, smooth, and glistening in the upper rectum and sigmoid colon, where the submucous vessels can be clearly seen. In the lower rectum the color is darker and the surface granular. Submucous vessels are not visible here.

Colored plates showing normal and pathologic sigmoidoscopic appearances were shown at the conclusion of the presentation.

A Biochemical Approach to the Chemotherapy of Cancer

Presented by DR. D. W. WOOLLEY (Rockefeller Institute for Medical Research, New York, N. Y.) before the American Chemical Society, New York, March 14, 1956.

Chemotherapy of cancer has at times been approached from the antimetabolite aspect. If we know the signs of deficiency of a product and then find a disease in which we have too much of the same, we try to induce a deficiency. In the chemotherapy of cancer, one must first see if the nutritional requirements of the cancer and the normal cell differ. With evolution, well differentiated organisms lose the ability to conduct many basic syntheses. Thus the higher animal must get its vitamins from its food, and antimetabolites of the vitamin precursors will not harm the host. To find the answer to whether the cancer cell has the ability to synthesize vitamins unlike the normal cells, it was decided to see if vitamin B_{12} and riboflavin were made by the spontaneous breast cancer tumor of the mouse.

Mother mice long deprived of B_{12} will not be able to provide their young, feeding on their milk, with B_{12}, as their stores are depleted and they cannot synthesize B_{12} themselves. The offspring manifest the deficiency by a slow rate of growth. These mice were then compared to mother mice with identical deficient diets but with breast cancers. In the latter group, despite the fact that no B_{12} was available to the mothers' diet or stores, the baby mice had essentially a normal rate of growth

This would indicate that B_{12} is being synthesized, and the only new factor is the breast cancer cells. Another piece of evidence that breast cancer cells in mice can produce vitamin B_{12} is seen in comparing the amount of B_{12} in the ground-up carcasses of mice who had long been deprived of B_{12}. Mice with cancer had a level of B_{12} twice that in nontumorous animals. With the knowledge that mice breast cancer cells might produce their own B_{12}, precursor analogues were then made. Relatively useful ones were hard to find as most analogues were quickly inactivated. However, when modified, activity seemed to be retained to some extent in the dimethyl diaminobenzene antagonists, dimethylaminophenol, and dichlorodinitrosulfa. These agents were used in mice with breast cancers, the experiment running over relatively long periods of time. One-third were never affected. In some, however, after three to four weeks on medication, the growth rate of the tumor began to slow, then stop. Sometimes, the tumor may soften and parts fall out through ulcerating skin. In addition to transient regression, some tumors undergo complete obliteration but usually appear again at a later date. In some rare cases, the mouse was declared completely cured, the growth having disappeared for at least five months. The drug was innocuous to the host, as these animals were able to maintain weight and even reproduce.

Hoping to convert the transient to complete cures, intermittent therapy was tried on the theory that resistant mutants may occur, but this did not generally change the results. Perhaps giving higher doses might result in more cures. If the dose is reduced one-third, we get no results at all. The dose of present drugs is high, i.e., 3 to 5 mg./day and is given as a poorly soluble injection. The dose of this agent cannot be increased. We need a stronger dose, and this can be gotten only with new drugs of this same type. A more active drug may enable us to cure all spontaneous mice breast cancers.

Hormonal Therapy of Breast Carcinoma

Presented by JULIAN B. HERRMANN, M.D., before the Montefiore Hospital Staff Conference, March 9, 1956.

Four per cent of women eventually develop carcinoma of the breast. For operable carcinoma, surgery is the therapy of choice, but about 20 per cent of the patients have an inoperable carcinoma when first seen. Of those patients who are operable, about one-half are dead or are living with disease five years after mastectomy and only 30 per cent are living, some with disease, 10 years after surgery. Thus about 75 per cent of the breast carcinoma patients require some form of therapy aside from or in addition to surgery.

Roentgenotherapy remains the bulwark for the treatment of inoperable or advanced disease and in general should be employed initially for soft-tissue lesions or discrete symptomatic osseous metastases. Widely disseminated disease requires hormonal therapy either alone or in conjunction with roentgenotherapy.

Castration, preferably surgical and otherwise roentgen castration combined with testosterone propionate, is the treatment of choice in menstruating women since about 30 to 35 per cent of mammary carcinomas are estrogen dependent and may be

expected to respond. There is no definite evidence that prophylactic castration, i.e., at the time of mastectomy, prevents or delays recurrences or metastases, and the premature use of castration may deprive the patient of a valuable therapeutic aid if and when recurrent or metastatic disease appears.

Androgenic hormone finds its greatest usefulness in the early postmenopausal women, especially those with osseous metastases and those who have not responded to castration or who have relapsed following a satisfactory castration effect. Testosterone propionate is the most efficient androgen yet employed, and 300 mg. a week in divided doses for a total of 3.5 Gm. is the most satisfactory dosage.

Estrogenic hormone finds its greatest usefulness in the patients who are at least five years postmenopause, especially those with soft-tissue metastases. A satisfactory estrogen is diethylstilbestrol, 5 mg. three times a day, continued as long as improvement is maintained.

Adrenocortical hormone will in some cases cause regression of metastatic lesions but is not as effective as the previously named hormones.

Adrenalectomy may be of value in patients who have benefited from castration but whose disease has become reactivated. There is no evidence at present that the combination of castration and adrenalectomy in menstruating women increases the number of patients benefited or the duration of improvement over that which could be expected from castration alone. Hence, in general, it is better to employ these modalities in sequence rather than concurrently in the women still in menstrual life. Adrenalectomy alone or combined with surgical castration may benefit some postmenopausal women.

Hypophysectomy is the most recent method of hormonal therapy, and its indications and value have yet to be established. Some investigators report about 30 to 40 per cent of patients improved symptomatically or objectively. This is approximately the percentage of patients benefited by the other hormonal modalities with the exception of cortisone.

The fundamental concept of hormonal therapy is that the disease cannot be eradicated by this form of treatment. Hence one treats the patient primarily and the disease secondarily. The endeavor is to keep the patient comfortable for as long a time as possible. For that reason, each patient must be individualized, and the therapeutic procedures, whether used singly or in combination, and the sequence employed must be adapted to the requirements of the individual patient to obtain the optimal results.

Pyuria in Infancy

Presented by VICTOR F. MARSHALL (Associate Professor of Clinical Surgery [Urology], Cornell University Medical College, and Attending Urologist, New York Hospital) before the Combined Sections on Pediatrics and Surgery, New York Academy of Medicine, February 9, 1956.

Pyuria is not a great rarity in the first two years of life; its onset after that is distinctly uncommon. The cases can be divided into two types: minor and major. Minor pyurias result essentially from contaminations. They are more common in

female infants, hence the necessity for catheterized specimens. Vaginitis may be the source of the pus. Minor pyuria should clear promptly within a week with such treatment as sulfisoxazole and local cleanliness. The urine should be checked after this period when the patient is believed to be well, and after six weeks to two months a follow-up examination should be done, even if the child is asymptomatic. A urinalysis and often a urine culture are called for then to determine that the infection is truly gone. If there is recurrence or persistence, a genitourinary check-up should be done and the case becomes major in type.

The causes in major cases are the same as in adults, but there are striking differences in the incidence of the causative factors. Urinary tuberculosis is rare in infants but well known as a cause of pyuria in adults. The cancers of childhood, such as Wilms's tumor, rarely produce pyuria. Calculi rarely cause pyuria in children in the United States. Obstruction from a malformation is overwhelmingly the most important cause. Urine becomes trapped and the organisms cannot escape. The kidneys may be destroyed by obstruction or infection alone, but these two together destroy rapidly—and they are usually together.

There are many different types of obstruction. Obstruction at the ureteropelvic junction, a common site, is often blamed on aberrant vessels. Obstruction at the junction of the bladder and the ureter may possibly be due to parasympathetic dysfunction as well as mechanical blocks. Secondary obstructions, especially in dilated and elongated ureters, may develop above the primary obstruction. In cases of the rare hypoplasia of the anterior abdominal wall, the genitourinary tract is usually badly affected. The obstructed ureter may become excessively long as well as dilated. The results of surgery to correct these huge ureters are usually poor. With a ureterocele there is a ballooning of the ureter into the bladder largely as a result of a pin-point (obstructing) orifice. Excellent results can usually be obtained by merely resecting the top of the protrusion, while an attempt to restore the appearance of normal anatomy may result in the loss of the valvelike action in the bladder wall, and ureteral reflux will appear. Double ureters often obstruct. Ureterocele is more common with double ureter. Obstructions occur at the vesical outlet comparatively frequently. Children with imperforate anus often have abnormal connections between the rectum and the genitourinary tract. This is usual in males with this anomaly. These children often have other genitourinary anomalies. In neurogenic bladder, such as occurs with meningomyelocele, many of these children have residual urine as well as leakage; an attempt to keep them dry with mechanical clamps on the urethra will aggravate infection, and some of these patients may require ureterostomies.

The intravenous urogram is of great value and should be used when there is any doubt as to diagnosis. Simple cystograms and/or urethrograms are often helpful. If there is ureteral reflux, you may get excellent retrograde filling. Complete cystoscopy is possible even in the newborn infant, but the male urethra is small, curved, delicate, and easily injured. It is often less traumatic to perform cystotomy for diagnostic measures than to pass instruments with difficulty through the urethra of the newborn male infant. Although it may be too late even at birth, the results are best when the diagnosis is reached early and proper therapy promptly instituted.

Intestinal Obstruction in the Newborn

Presented by THOMAS V. SANTULLI (Chief of Pediatric Surgery, Babies and Presbyterian Hospital, New York, N. Y.) before the Combined Sections on Pediatrics and Surgery, New York Academy of Medicine, February 9, 1956.

This report is based on 207 consecutive cases of intestinal obstruction seen in the neonatal age group from 1939 to 1955. This series excludes lesions of the esophagus, stomach, and rectum. It includes lesions of the small and large bowel. All diagnoses were proved at operation or autopsy. Early diagnosis is the most important single factor affecting prognosis. Any newborn infant who vomits, especially bile, is suspect and should have three position plain roentgenograms of the abdomen. There is special danger in premature infants because they often fail to develop peritoneal signs.

There are two broad groups of intestinal obstruction: mechanical and neurogenic. In the mechanical group, gangrene of the testis in incarcerated hernia may be seen and is not often thought of. The mortality in the entire group is 42 per cent. Congenital atresia or stenosis of the colon is very rare. Malrotation may obstruct the superior mesenteric vessels and cause gangrene of the mid-gut. In meconium ileus, characteristically the terminal ileum is plugged with abnormal meconium. There is hypertrophy proximally. The colon is small, and the terminal ileum contains small concretions. Viscid meconium fills the dilated proximal part. Of 37 cases we have seen of this disease, only 4 are still alive. The others died of respiratory infection. If they live long enough, they show the generalized disease that is associated with cystic fibrosis of the pancreas.

Twenty-eight newborn infants with intestinal obstruction were admitted and were found to have megacolon. Colostomy is the treatment of choice, followed later by resection and "pull-through." There were eight deaths. Four of those who died of megacolon had membranous colitis not associated with antibiotic therapy.

The over-all mortality used to be about 60 per cent but is now 30 to 35 per cent. One important factor is the routine use of adequate proximal decompression. Leakage at the suture line is a common cause of death.

Endometriosis as a Cause of Intestinal Obstruction

Presented by PAUL MCGUFF, M.D., M.S. (SURG.), before the Pan American Congress of Physical Medicine, San Juan, Puerto Rico, January 29–February 8, 1956.

Endometriosis as a cause of intestinal obstruction may produce complete or incomplete intestinal obstruction. The most commonly affected sites are the rectum, sigmoid flexure, and terminal ileum. There are three theories as to the pathogenesis of endometriosis: first, that the condition has an embryonic origin; second, that the condition is metaplastic in origin; third, that it is of migratory origin with lymphatic or venous spread.

As to the signs and symptoms when intestinal obstruction is present, the patient may have abdominal pain, tenderness, vomiting if obstruction is high, constipation if obstruction is low, dysmenorrhea, menorrhagia, metrorrhagia, and accentuated pelvic pain when walking in high heels.

Adjuncts to diagnosis include digital examination, sigmoidoscopy, roentgenograms of the gastrointestinal tract, and biopsy of the vaginal vault when possible.

The treatment in young women is intestinal resection with or without oophorectomy; in older women, conservative treatment of the bowel with panhysterectomy. In other words, in young women use conservative treatment of the genital tract and radical treatment of the bowel, but in older women use radical treatment of the reproductive system with conservative surgery of the bowel.

Effect of Vascular Collapse on Infection by Microorganisms

Presented by JACOB FINE, M.D., (Beth Israel Hospital, Boston, Mass.) before the New York Society of Physical Chemists, New York Academy of Science, January 31, 1956.

By use of a bottle that may be raised to any given height above the heart of an experimental animal, it is possible to bleed an animal into the bottle to any desired blood pressure. We used this method to produce shock in dogs for given periods of time, utilizing a blood pressure of 30 mm. of mercury. We found that if the blood in the bottle is returned to the dog after two hours, the blood pressure will return to normal and the dog will survive. But if the blood pressure is kept at 30 mm. of mercury for much longer than two hours, i.e., for four to five hours, the rise in blood pressure following return of all the blood in the bottle will not be sustained.

When dogs were treated with antibiotics prior to the bleeding, the development of irreversibility to the transfusion was delayed or prevented. Such treated dogs were able to survive if transfused after as many as eight hours of shock. When the tissues of the untreated dogs were cultured just after death, various intestinal flora were recovered. Except for clostridia, these were not found during life in these dogs. The author believes that these bacteria are not solely agonal invaders from the gastrointestinal tract, but continuously invade during life in the normal as well as the shocked dog.

Experiments were carried out to test the tissue function of shocked dogs. Thus, it was found that 60 to 90 hours is needed by normal animals to restore the plasma prothrombin activity to normal after lowering it to 0 per cent. But dogs subjected to two hours of shock required 180 hours or more to restore the depleted prothrombin activity to normal. Such findings suggest that there is a breakdown of tissue integrity, which probably involves all kinds of tissue functions, including the mechanism for defense against bacteria. To test the latter inference, the dog's ability to handle intravenously injected bacteria was studied. It was found that a normal dog will tolerate an induced bacteremia, which a shocked dog cannot tolerate. It has been shown further that the shocked animal is extremely hypersensitive to bacterial toxin. Thus, a rabbit recovering from two hours of shock is 100,000 times more sensitive than a normal rabbit to a standardized dose of bacterial toxin.

Experiments were done that identified the presence of a bacterial factor in shocked dogs that is not present in normal dogs. Liver mash was injected into the peritoneal cavity of normal and shocked dogs. Liver mash from normal dogs did not kill normal or shocked dogs. Liver mash from shocked dogs did not kill normal dogs, but did kill shocked dogs. But if the latter were given penicillin, they survived. Thus, there must be a bacterial factor in the liver mash taken from shocked dogs.

Bacterial toxin that kills every rabbit injected with it kills only half of them if an antibiotic is given prior to the toxin injection. Hence bacterial activity contributes to the death of the animal following the injection of bacterial toxin. The most likely source of the bacteria involved is the gastrointestinal tract, because the protection against toxin is obtained even when a nonabsorbable antibiotic given orally (bacitracin and polymyxin B) is used.

The shocked animal's serum contains a factor that inhibits the action of phagocytes and depresses their capacity to destroy ingested bacteria.

The acid phosphatase and β-glucuronidase content of phagocytes from shocked rabbits is less than that of phagocytes from normal rabbits.

The Properdin titer falls to zero or near zero in shock. There is no change in serum complement levels of shocked animals. We found that there was no fall in serum Properdin titer if animals were cooled before the shock was induced.

Experiments were also done that demonstrate that precooling will protect the animal from the deleterious effects of shock.

Coronary Artery Disease

Presented by PAUL D. WHITE (Professor Emeritus of Medicine, Harvard School of Medicine) before the Boston City House Officers Association, January 10, 1956.

Commonly, coronary artery disease is not a chronic, unchanging disease. This concept is very important to remember in evaluating therapeutic measures. Often therapeutic credit is given to normal improvement. The disease occurs in all degrees, from angina pectoris to massive myocardial infarction. Many persons with coronary artery disease have an excellent or good prognosis. Coronary artery disease has no respect for person, age, or sex, except that young and middle-aged males are much more often affected than are young and middle-aged females. Research will give the answer to many questions in the near future.

Coronary atherosclerotic heart disease (ischemic heart disease) includes angina pectoris, coronary occlusion, and myocardial infarction, as well as the term "coronary insufficiency," one manifestation of which is angina pectoris. One can have extensive atherosclerosis, calcification, and insufficiency, as well as occlusion of the coronary arteries, without symptoms. Almost all heart disease is basically a vascular disorder and not a disease of the myocardium per se. Angina pectoris occurs in all degrees, from very mild substernal pain on exertion to angina decubitus with symptoms at rest. The latter represents a dangerous threat to the patient, and these patients must be carefully watched, while mild symptoms require very little alteration in the patient's life. Occlusion may or may not result in infarction. Infarction

occurs in various areas of the heart and may reoccur; complete occlusion need not be present as a cause thereof if there is sufficient narrowing of a coronary artery segment.

A good medical history is of the greatest importance. The electrocardiogram has also become of great value in the diagnosis. It is also of much importance not to overdiagnose this disease because of the great range of normal patterns that occur in the electrocardiogram. There are a few cases of silent ischemia picked up by the electrocardiogram, and not infrequently bundle branch blocks are seen in patients without symptoms of heart disease. Bundle branch block with no other symptoms generally indicates coronary heart disease, but in these cases the author advocates a "common sense life." Many patients with coronary heart disease have normal heart size, normal sounds, and normal blood pressure. Hypertension definitely aggravates coronary heart disease, but the two are separate diseases.

Nitrites are spectacular in their temporary relief of symptoms and may be life-saving. Other methods have come and gone. Diets have been tried and, in the speaker's experience, generally with no specific results. As yet there is nothing adequate for the treatment of coronary heart disease, mending the myocardium more rapidly, or shrinking the area of necrosis. Blumgart's use of irradiated iodine in selected cases has been helpful. Alcohol injections and sympathectomy have mostly been abandoned. The value of surgical measures is as yet not clearly proved, although Blumgart advocates further research in this field. His primary objection to surgical research in the field to date is twofold: the lack of adequate controls and the failure to demonstrate adequate myocardial vascularity on the basis of the surgical operations. Patients who have myocardial infarction may have an extensive pericarditis. In these there exists the possibility of increased vascularity, as yet, however, unproved. No one, to the speaker's knowledge, has studied these patients to find out if this factor has any prognostic value. Most surgical procedures produce a sterile pericarditis as the rationale for the procedure.

More epidemiologic research is necessary to study both basic and environmental factors. Diet, a factor that is being well studied, may or may not be the hub of the problem. There are as yet not careful enough studies of races living under all sorts of conditions to evaluate the problem adequately. Results to date indicate that race itself is not important. Mesomorphs are more likely candidates for coronary heart disease than persons with other body builds, at least in the younger groups. There is a higher incidence of coronary heart disease in aggressive personality types and in those with increased cholesterol levels. Stress and strain as environmental factors are difficult to define and measure. In doing so, one should grade the sensitivity of the individual as well as the degree of the stress. Whether exercise has any corrective or beneficial influence is not really known. Theoretically, if a person exercises and burns all the fat intake, there is less left in the body to increase the serum cholesterol. A recent study in Naples, Italy, revealed that the serum cholesterol levels of steelworkers and office clerks were almost the same. It is not known whether the total fat intake or the type of fat is the most important consideration. The role of proteins and carbohydrates in the development or retardation of coronary heart disease is not known.

BIBLIOGRAPHY

(*Article appears on page 642.*)

1. FISCHEL, E. E.; FRANK, C. W., AND RAGAN, C.: Observations on the treatment of rheumatic fever with salicylate, ACTH, and cortisone, Medicine *31*:331–335, 1952.
2. REID, J.; WATSON, R. D., AND SPROULL, D. H.: The mode of action of salicylates in rheumatic fever, Quart. J. Med. (New Series) *19*:1–20, 1950.
3. CALESNICK, B., AND BEUTNER, R.: Inhibition of hyaluronidase by aromatic compounds, Proc. Soc. Exper. Biol. & Med. *72*:629–632, 1949.
4. BLANCHARD, K. C.; DEARBORN, E. H.; MARAN, T. H., AND MARSHALL, E. K.: Stimulation of the anterior pituitary by certain cinchoninic acid derivatives, Bull. Johns Hopkins Hosp. *86*:83–88, 1950.
5. COCHRAN, J. B.; WATSON, R. D., AND REID, J.: Mild Cushing's syndrome due to aspirin, Brit. M. J. *2*:1411–1413, 1950.
6. CRONHEIM, G., AND KING, J. S., JR.: The ACTH-like action of salicylic acid, J. Pharmacol. & Exper. Therap. *103*:341, 1951.
7. KELEMEN, E.; MAJOROS, M., AND TANOS, B.: Salicylates in acute osteomyelitis, Lancet *2*:457, 1950.
8. PASQUALINI, R. Q.; DE PASQUALINI, C. D., AND GARBERI, J. C.: Accion del salicilato de sodio sobre el sistema hipofiso-suprarenal, Rev. Soc. argent. de biol. *26*:120–126, 1950 (cf. Compt. rend. Soc. de biol. *145*:122–125, 1951).
9. ROBINSON, F. B.: Aspirin and the adrenal cortex, Brit. M. J. *1*:300, 1950.
10. CAUWENBERGE, H. VAN: Relation of salicylate action to the pituitary gland. Observations in rats, Lancet *2*:374–375, 1951.
11. HETZEL, B. S., AND HINE, D. C.: The effects of salicylates on the adrenal and pituitary glands, Lancet *2*:94–97, 1951.
12. KING, J. S., JR.: Part I. The action of salicylate as related to pituitary-adrenal function, Ph.D. thesis, Univ. Tennessee, Memphis, 1954.
13. FISCHEL, E. E.: The use of salicylate in rheumatic fever, Bull. Rheumat. Dis. *2*:9–10, 1952.
14. SELYE, H.: First Annual Report on Stress—1951, Montreal, Acta, Inc., 1951.
15. COBURN, A. F.: Salicylate therapy in rheumatic fever. A rational technique, Bull. Johns Hopkins Hosp. *73*:435–464, 1943.
16. JAGER, B. V., AND ALWAY, R.: The treatment of acute rheumatic fever with large doses of sodium salicylate, with special reference to dose management and toxic manifestations, Am. J. M. Sc. *211*:273–285, 1946.
17. MANCHESTER, R. C.: Rheumatic fever in naval enlisted personnel. II. Effectiveness of intensive salicylate therapy in cases of acute infection, Arch. Int. Med. *78*:170–180, 1946.
18. CRONHEIM, G.; KING, J. S., JR., AND HYDER, N.: Effect of salicylic acid and similar compounds on the adrenal-pituitary system, Proc. Soc. Exper. Biol. & Med. *80*:51–55, 1952.
19. LOWENTHAL, J., AND JACQUES, L. B.: A comparative study of the effect of a series of aromatic acids on the ascorbic acid content of the adrenal gland, J. Pharmacol. & Exper. Therap. *107*:172–177, 1953.
20. ROSKAM, J., AND CAUWENBERGE, H. VAN: Cortisone, ACTH et salicylés dans le traitement des rheumatismes inflammatoires et des états similaires, Presse méd. *60*:1344–1347, 1952.
21. CAMELIN, A.; ACCOYER, P.; VAILHE, J.; ROUMAGNAC, H., AND ROSSET, B.: Treatment of acute rheumatism in adults with sodium salicylate or gentisate. Six years hospital experience, J. de méd. de Lyon *33*:643–644, 1952.
22. Joint Committee of Medical Research Council and Nuffield Foundation: A comparison of cortisone and aspirin in the treatment of early cases of rheumatoid arthritis, Brit. M. J. *1*:1223–1227, 1954; *2*:695–700, 1955.
23. COSTE, F., AND LACRONIQUE, F.: Traitements hypophysosurrénaux des polyarthrites chroniques évolutives et de la spondylarthrite ankylosante (en dehors de la cortisone et de l'ACTH), Ann. Rheumat. Dis. *9*:305–316, 1950.

24. Lee, R. E., and Pfeiffer, C. C.: Effects of cortisone and 11-desoxycortisone on pain thresholds in man, Proc. Soc. Exper. Biol. & Med. *77*:752–754, 1951.
25. Kelemen, E.; Majoros, M.; Ivanyi, J., and Kovacs, K.: Salicylates, cortisone, and stress, Experientia *6*:435, 1950.
26. Sonnenchein, R. R., and Ivy, A. C.: Failure of oral antipyretic drugs to alter normal human pain thresholds, J. Pharmacol. & Exper. Therap. *97*:308–313, 1949.
27. Gifford, S. R.: The use of drugs in ophthalmology, J. A. M. A. *113*:928–930, 1939.
28. Bach, F.; Freedman, A., and Bernstock, L.: Rheumatic fever: some observations on ACTH, cortisone, and salicylate therapy, Brit. M. J. 2:582–587, 1952.
29. Gordon, G.; Li, C. H., and Bennett, L. L.: Effect of adrenocorticotrophic hormone on urinary nitrogen excretion in the normal rat, Proc. Soc. Exper. Biol. & Med. *62*:103–105, 1946.
30. Sprague, R., and Power, M. H.: Metabolic effects of cortisone and ACTH in cases of rheumatoid arthritis. *In:* Proc. Clin. ACTH Conf., 1st Conf., Philadelphia, Blakiston Co., 1950, pp. 363–385.
31. Reifenstein, E. C., Jr.: The protein anabolic activity of steroid compounds. *In:* Conf. on Bone and Wound Healing, Minutes (Supplement), New York, Josiah Macy, Jr., Foundation, 1942.
32. Bardawill, C. J.; Gornall, A. G.; Nishikawara, M., and Wightman, K. J. R.: Studies on the behaviour of urinary amino nitrogen, serum alkaline phosphatase, and pseudo cholinesterase activity during ACTH therapy. *In:* Proc. Clin. ACTH Conf., 1, 2nd Conf., Philadelphia, Blakiston Co., 1951, pp. 264–272.
33. Borden, A. L.; Brodie, E. C.; Wallraff, E. B.; Holbrook, W. P.; Hill, D. F.; Stephens, C. A. L., Jr.; Johnson, R. B., and Kemmerer, A. R.: Amino acid studies and clinical findings in normal adults and rheumatoid arthritis patients treated with ACTH, J. Clin. Invest. *31*:375–379, 1952.
34. Milhaud, G., and Doret, J. P.: Effet de la cortisone sur l'élimination urinaire des acids amines. Schweiz. med. Wchnschr. *81*:953–956, 1951 (cf. Milhaud, G.: Praxis *10*:196, 1952).
35. Ronzoni, E.; Roberts, E.; Frankel, S., and Ramasarma, G. B.: Influence of administration of ACTH on urinary amino acids, Proc. Soc. Exper. Biol. & Med. *82*:496–503, 1953.
36. Simões, M. S., and de Barros, J. P.: Salicylatos e aminoacidúria, Portugal méd. *39*:271–276, 1955.
37. Bertolani, F.; Bonati, B.; Lorenzini, R.; Bergamini, A., and Mari, E.: Salicylici, ipofisi e corticosurrene, Folia endocrinol. *6*:61–81, 1953.
38. Harris, T. N.: The failure of massive salicylate therapy to suppress the inflammatory reaction in rheumatic fever, Am. J. M. Sc. *213*:482–487, 1947.
39. Homburger, F.: The effect of sodium salicylate on the sedimentation rate of erythrocytes *in vivo*, Am. J. M. Sc. *211*:346–349, 1946.
40. Lichty, J. A., Jr., and Hooker, S. P.: Effect of acetyl salicylic acid on sedimentation rate of erythrocytes in rheumatic fever, Proc. Soc. Exper. Biol. & Med. *48*:69–70, 1941.
41. Bertolani, F.; Mari, E., and Luiani, G.: Azione di alcune sostanze aromatiche della serie del benzolo sulla velocitá di sedimentazione degli eritrociti, Arch. per le sc. med. *93*:1–22, 1952.
42. Germuth, F. G., Jr.; Nedzel, G. A.; Ottinger, B., and Oyama, J.: Anatomic and histologic changes in rabbits with experimental hypersensitivity treated with Compound E and ACTH, Proc. Soc. Exper. Biol. & Med. *76*:177–182, 1951.
43. Smull, K.; Wissler, R. W., and Watson, J. M.: The effect of sodium salicylate upon serum disease in rabbits, J. Lab. & Clin. Med. 33:936–950, 1948.
44. Smith, W., and Humphrey, J. H.: The effect of sodium salicylate upon hypersensitivity reactions, Brit. J. Exper. Path. *30*:560–571, 1949.
45. Fischel, E. E.: Effect of salicylate and tripelennamine hydrochloride (Pyribenzamine) on the Arthus' reaction and on bacterial allergic reactions, Proc. Soc. Exper. Biol. & Med. *66*:537–541, 1947.
46. Ungar, G.; Damgaard, E., and Weinstein, H. G.: Anaphylactic arthritis in guinea pigs and its hormonal control, Federation Proc. *10*:422, 1951.
47. Schwartzman, G.; Schneierson, S. S., and Soffer, L. J.: Suppression of the phenomenon of local tissue reactivity by cortisone, ACTH, and sodium salicylate, Proc. Soc. Exper. Biol. & Med. *75*:175–178, 1950.
48. Betz, H., and Cauwenberge, H. Van: Réactions histologiques á l'injection de salicylate de soude chez le rat, Compt. rend. Soc. de biol. *145*:1275–1277 (see also 1439–1442), 1951.

49. Kelemen, E., and Majoros, M.: Salicylate, gentisate, and circulating eosinophils, Lancet *1*:962, 1951.
50. Pasqualini, R. Q.: Eosinopenia salicilica, Prensa méd. argent. *39*:490–495, 1952.
51. Roskam, J., and Cauwenberge, H. Van: Cortisone, ACTH, et salicylés dans le traitement des rheumatismes inflammatoires et des états similaires, Presse méd. *60*:1344–1347, 1952.
52. Kelemen, E.; Majoros, M.; Soltesz, R., and Tanos, B.: Zum Wirkungmechanismus grosser Salicylatdosen, Deutsche med. Wchnschr. *77*:1317–1320, 1952.
53. Rivi, E.: Recerca sul meccanismo dell'azione antireumatica del salicilato, Boll. Soc. med.-chir. Modena *51*:253, 1951.
54. Meade, B. W., and Smith, M. J. H.: Salicylates, gentisates, and circulating eosinophils, Lancet *1*:236, 1951.
55. Comulada, G. M.; Pierre-Em, C., and Smith, P. K.: Action of salicylates and related compounds on carbohydrate metabolism and on adrenal ascorbic acid and cholesterol concentrations, Federation Proc. *12*:313, 1953 (cf. J. Pharmacol. & Exper. Therap. *114*:299–305, 1955).
56. Roskam, J.; Cauwenberge, H. Van, and Mutsers, A.: Effect of sodium salicylate on circulating eosinophils and urinary uric acid: creatinine ratio, Lancet *2*:375–376, 1951.
57. Kelemen, E.: Screening tests for anti-rheumatic substances, Acta Med. Acad. Sc. Hung. *3*:369–376, 1952.
58. Hardy, J. D.: Surgery and the Endocrine System, Philadelphia, W. B. Saunders Co., 1952, pp. 4–5.
59. Harris, M. M., and Lang, B.: Effect of administration of amino acids on circulating eosinophils and lymphocytes in normal and adrenalectomized rats, Proc. Soc. Exper. Biol. & Med. *80*:664–667, 1952.
60. Tanos, B.; Szilasy, S.; Varro, V.; Eisner, A., and Olah, F.: A humoral agent with immediate eosinopenic effect other than cortisone, Experientia *9*:266–267, 1953.
61. Muehrcke, R. C.; Staple, T. W., and Kark, R. M.: Epinephrine eosinopenia in surgically induced Addison's disease, J. Lab. & Clin. Med. *40*:169–173, 1952.
62. Gelli, G. P., and Della Santa, L.: L'azione del cortisone sulle concentrazioni ematiche del salicilato di sodio, Minerva pediat. *7*:1456, 1955.
63. Guerra, F.: Response of experimental arthritis with different levels of pharmacologic integration in the rat, Federation Proc. *12*:326–327, 1953.
64. Janbon, M.; Bertrand, L.; Salvaing, J., and Lebauge, R.: Le traitement hormono-salicyle de la maladie de Bouillaud, Presse méd. *59*:1344, 1951.
65. Fischel, E. E., and Frank, C. W.: Report to First Interim Session of Amer. Rheumatism Assoc., 1954.
66. Busse, E. A.: Treatment of rheumatoid arthritis by a combination of cortisone and salicylates, Clin. Med. *2*:1105–1108, 1955.
67. Spies, T. D.; Stone, R. E.; Lopez, G. G.; Tellechea, C. M. D.; Toca, R. L.; Reboredo, A., and Suárez, R. M., Sr.: Predisone and prednisolone as therapeutic agents: progress report on their integration into general medical practice, J. A. M. A. *159*:645–652, 1955.
68. Montuori, E., and Balla, J.: Action de la cortisone sur la toxicité du salicylate de soude, Compt. rend. Soc. de biol. *148*:1640–1642, 1954.
69. Sayers, G., and Sayers, M. A.: The pituitary-adrenal system, Ann. New York Acad. Sc. *50*:522–539, 1949.
70. Cauwenberge, H. Van; Betz, H.; Heusohem, C., and Vliers, M.: Salicyles non éminces, para-aminosalicylate de soude et cortex surrénalien, Ann. d'endocrinol. *12*:788–792, 1951.
71. Cauwenberge, H. Van, and Heusohem, C.: Modifications biochémiques de la surrénale après injection de salicylate de soude chez le rat, Compt. rend. Soc. de biol. *145*:1272–1275, 1951.
72. Coste, F.; Bourel, M., and Delbarre, F.: Depletion of adrenal ascorbic acid under the influence of sodium salicylate in the hypophysectomized rat, Compt. rend. Soc. de biol. *147*:668–669, 1953.
73. Petersen, P. V.; Weidmann, H., and Moller, E.: Effect of various new synthetic compounds on adrenal ascorbic acid, Acta pharmacol. et toxicol. *11*:103–110, 1955.
74. Cronheim, G.; King, J. S., Jr., and Hyder, N.: Effect of salicylic acid on the adrenal pituitary system. II. Influence of amino acids and other compounds, Proc. Soc. Exper. Biol. & Med. *82*:109–111, 1953.
75. Cronheim, G.; King, J. S., Jr., and Hyder, N.: The effect of salicylates on the adrenal-pituitary system, Abstracts, XIX Internat. Physiol. Cong., Montreal, 1953, pp. 290–291.

76. Done, A. K.: Personal communication.
77. Stenger, E. G.; Mosdorf, K., and Domenjoz, R.: Der Zusammenhang zwischen Ascorbinsaure und Cholesterindepletion in der Nebenniere, Arzneim.-Forsch. 5:489–490, 1955.
78. Bonati, B.; Bertolani, F., and Lorenzini, R.: Action of some hydroxy aromatic acids on the excretion of 17-ketosteroids and on the circulating eosinophils, Farm. sci. e tec. 6:719–725, 1951.
79. Roskam, J.; Cauwenberge, H. Van; Vivario, R., and Vliers, M.: Action mechanisms of salicylate therapy, Presse méd. 63:1105–1107, 1955.
80. Tronchetti, F., and Nello, R. P.: Sodium salicylate and the urinary excretion of corticosteroids, Folia endocrinol. 4:663–671, 1951.
81. Done, A. K., and Kelley, V. C.: Summary, 2nd Interim Scientific Session of the American Rheumatism Association, Bull. Rheumat. Dis. 6:105–106, 1956.
82. Cauwenberge, H. Van, and Heusghem, C.: Thérapeutique par acide acetysalicylique et excrétion urinaire des corticosteroids, Acta med. Scandinav. 141:265–283, 1951 (cf. Lancet 1:771, 1951).
83. Done, A. K.; Ely, R. S., and Kelley, V. C.: Studies of 17-hydroxycorticosteroids. III. Blood levels in salicylate intoxication, J. Pediat. 44:153–158, 1954.
84. Henly, A. A.: Steroid metabolism in rheumatoid arthritis, Ann. Report, West London Hosp., pp 24–26, 1952.
85. Bayliss, R. I. S., and Steinbeck, A. W.: Salicylates and the plasma levels of adrenal steroids, Lancet 1:1010–1111, 1954.
86. Coste, F.; Bourel, M.; Delbarre, F., and Weissenbach, R.: Comment agit le salicylate de sodium? Presse méd. 61:979–982, 1953.
87. Smith, M. J. H.; Gray, C. H., and Lunnon, J. B.: Urinary excretion of adrenocortical steroids by patients receiving salicylates, Lancet 1:1008–1009, 1954.
88. Done, A. K.; Ely, R. S.; Raile, R. B., and Kelley, V. C.: Studies of 17-hydroxysteroids. XIII. Effects of salicylate intoxication in rheumatic and non-rheumatic subjects, J. Pediat. 47:727–732, 1955.
89. Lutwak-Mann, C.: The effect of salicylates and cinchophen on enzymes and metabolic processes, Biochem. J. 36:706–728, 1942.
90. Sproull, D. H.: The glycogenolytic action of sodium salicylate, Brit. J. Pharmacol. 9:121–124, 1954.
91. Ingle, D. J.: Effect of aspirin upon glucosuria of the partially depancreatized rat, Proc. Soc. Exper. Biol. & Med. 75:673–675, 1950.
92. Ingle, D. J.: Effects of salicylate on glucosuria and hyperglycemia, induced by cortisone in the normal rat, Biochem. J. 53:649–651, 1953.
93. Smith, M. J. H.; Meade, B. W., and Bornstein, J.: The effect of salicylate on glycosuria, blood glucose, and liver glycogen in the alloxan-diabetic rat, Biochem. J. 51:18–20, 1952.
94. Eichler, O., and Bengeforth, F.: Effect of salicylates on carbohydrate and fat metabolism, Arch. f. exper. Path. u. Pharmakol. 188:255–264, 1938.
95. Appel, S. B.; Gluck, J. L.; Reichman, S.; Miller, A.; Goldman, A.; Springer, C.; Schlecker, A. A.; Rosenbluth, M. B., and Kupperman, H. S.: Effect of ACTH on blood glucose and insulin hypoglycemia, Federation Proc. 11:318, 1952.
96. Ingle, D. J.; Beary, D. F., and Purmalis, A.: The effect of aspirin upon the glycosuria of partially depancreatized rats in the presence and absence of adrenal glands, Endocrinology 52:403–406, 1953.
97. Smith, M. J. H., and Irving, J. D.: The effect of salicylate on the passage of a barium meal in the rat, Brit. J. Radiol. 28:39–41, 1955.
98. Smith, M. J. H.: Effect of salicylate on liver glycogen in the rat, Biochem. J. 57:349–352, 1954.
99. Smith, M. J. H.: The effects of sodium salicylate on blood glucose in the rat, Brit. J. Pharmacol. 10:110–112, 1955.
100. Smith, M. J. H.: The effect of salicylate on glucose tolerance in the rat, Biochim. Biophys. Acta 14:241–245, 1954.
101. Nelson, C. T.; Fox, C. L., and Freeman, E. B.: Inhibitory effect of cortisone on anaphylaxis in the mouse, Proc. Soc. Exper. Biol. & Med. 75:181–183, 1950.
102. Selye, H.: Effect of ACTH and cortisone upon an "anaphylactoid reaction," Canad. M. A. J. 61:553–556, 1949.
103. Campbell, B.: Inhibition of anaphylactic shock by acetylsalicylic acid, Science 108:478–479, 1948.
104. Lepper, M. H.; Caldwell, E. R., Jr.; Smith, P. K., and Miller, B. F.: Effects on anaphylactic

shock of salicylates, aminopyrine, and other chemically and pharmacologically related compounds. Proc. Soc. Exper. Biol. & Med. *74*:254–258, 1950.
105. Humphrey, J. H.: Effect of cortisone on experimental hypersensitivity reactions, Brit. J. Exper. Path. 32:274–283, 1951.
106. Thierlot, J.; Simon, E.; LaForet, J., and Berthelay, J.: Influence du salicylate et du gentisate de sodium sur la perméabilité de la membrane synoviale de l'articulation, Compt. rend. Acad. d. sc. *232*:1612–1614, 1951.
107. Guerra, F.: Hyaluronidase inhibition by sodium salicylate in rheumatic fever, Science *103*:686–687, 1946.
108. Swyer, G. I. M.: Failure of *in vitro* inhibition of hyaluronidase by salicylates, Biochem. J. *42*:32–35, 1948.
109. Pasqualini, R. Q.; de Pasqualini, C. D., and Garberi, J. C.: Action of sodium salicylate on the pituitary-adrenal system, Compt. rend. Soc. de biol. *145*:122–125, 1951.
110. Pelloja, M.: Rôle of the pituitary and adrenal glands in the inhibition of hyaluronidase by salicylates in vivo, Lancet *1*:233–236, 1952.
111. Calbinick, B., and Beutner, K. R.: Relation of chemical structure to the action of hyaluronidase inhibitor, Federation Proc. *8*:278, 1949.
112. Kelemen, E.: The rôle of cortisone in a permeability response of salicylate-injured adrenalectomized rats, Acta Med. Acad. Sc. Hung. *9*:125–132, 1956.
113. Bywaters, E. G. L.; Holborow, E. J., and Keech, M. K.: Reconstitution of the dermal barrier to dye spread after hyaluronidase injection, Brit. M. J. 2:1178–1183, 1951.
114. Jaworski, A. A.; Farley, J. E.; Barbet, J., and Jaworski, A.: Relation of hyaluronidase to salicylates and rheumatic fever, J. Pediat. *37*:697–708, 1950.
115. Schuman, C. R., and Finestone, R. J.: Inhibition of hyaluronidase *in vivo* by adrenal cortical activation, Proc. Soc. Exper. Biol. & Med. *73*:248–251, 1950.
116. Cauwenberge, H. Van, and LeCompte, J.: Tests de diffusion, salicylés et hormones hypophyso-surrénaliennes, Experientia *9*:146–147, 1953.
117. Cauwenberge, H. Van, and LeCompte, J.: Corticostimuline (A.C.T.H.), hormones, corticales, salicylés et diffusion intradermique sous l'influence de l'hyaluronidase, Ann. Soc. belge d'endocrin. *15*:373–385, 1954.
118. Bianchi, C.: Experimental observations on a test for synovial permeability, Brit. J. Pharmacol. *8*:130–133, 1953.
119. Champy, C., and Demay, L.: Le mode d'action des salicylates (et analogues) se remaine-t-il à une action endocrine spécifique? Bull. Acad. nat. méd. *135*:13–17, 1951.
120. Zizine, L. A.: Action of sodium salicylate on adrenal atrophy produced by cortisone, Compt. rend. Soc. de biol. *147*:1577–1579, 1953.
121. Halpern, B. N.; Gaudin, O.; Stiffel, C., and Samarcq, R. P.: Action inhibitrice des sels de l'acide salicylique administrés par voie percutanée sur l'atrophie corticosurrénalienne provoquée par la cortisone, Compt. rend. Soc. de biol. *148*:1050–1053, 1954.
122. Selye, H.: Further studies concerning the participation of the adrenal cortex in the pathogenesis of arthritis, Brit. M. J. 2:1129–1135, 1949.
123. LaBelle, A., and Tornaben, J. A.: Effects of various analgesics on inflammatory edema resulting from silver nitrate injection, Science *114*:187–188, 1951.
124. Guerra, F.: The action of sodium salicylate and sulfadiazine on hyaluronidase, J. Pharmacol. & Exper. Therap. *87*:193–197, 1946.
125. Bacchus, H., and Bacchus, A.: Effect of aspirin on formalin-arthritis in normal and adrenalectomized rats, Federation Proc. *12*:7, 1953.
126. Coburn, A. F., and Haninger, J.: The serum diphenylamine (DPA) reaction in experimental arthritis, J. Exper. Med. *99*:1–19, 1954.
127. Cauwenberge, H. Van, and LeCompte, J.: Action antiinflammatoire comparée de l'ACTH, de la cortisone, et du salicylate de soude, Experientia *8*:469–471, 1952.
128. Selye, H.: Personal communication.
129. Cronheim, G., and Hyder, N.: Effect of salicylic acid on the adrenal-pituitary system. III. Studies on the mechanism of this effect, Proc. Soc. Exper. Biol. & Med. *86*:409–413, 1954.

130. Betz, H.: Influence de l'ACTH sur la mortalité des souris irradiées, Compt. rend. Soc. de biol. *145*:1240–1242, 1950.
131. Betz, H., and Cauwenberge, H. Van: Influence du salicylate de sodium sur la résistance des souris irradiées par les rayons X, Compt. rend. Soc. de biol. *145*:1910–1913, 1950.
132. Eades, C. H., Jr., and King, J. S., Jr.: Detectable amounts of ACTH in blood following salicylate administration, Endocrinology *52*:524–526, 1953.
133. Meyers, W. M., and Lysenko, M. G.: Effect of sodium salicylate treatment on antibody titers in rats infected with *Trypanosoma lewisi*, Proc. Soc. Exper. Biol. & Med. *84*:97–98, 1953.
134. Fischel, E. E.: Relation of adrenal cortical activity to immune responses, Bull. New York Acad. Med. *26*:255–260, 1950.
135. Market, S., and Harois, B. J.: The effect of ACTH and cortisone on the quantitative precipitin reaction, J. Immunol. *69*:217–221, 1952.
136. Little, J. M.; Strader, E. R., and Truitt, E. B.: The relation between the structure of halogenated benzoic acids and the depletion of adrenal ascorbic acid, J. Pharmacol. & Exper. Therap. *112*:378–381, 1954.
137. Lowenthal, J., and Jacques, L. B.: A comparative study of the effect of a series of aromatic acids on the ascorbic acid content of the adrenal gland, J. Pharmacol. & Exper. Therap. *107*:172–177, 1953.
138. Reid, J.; Watson, R. D.; Cochran, J. B., and Sproull, D. H.: Sodium γ-resorcylate in rheumatic fever, Brit. M. J. 2:321–325, 1951.
139. Smith, M. J. H.: Monohydroxybenzoic acids and ascorbic acid depletion of the adrenal glands of the intact rat, Lancet *1*:991–993, 1952.
140. Cauwenberge, H. Van: Reaction of the hypothalamic-hypophyseal-adrenal axis to some benzene derivatives, Compt. rend. Soc. de biol. *145*:1118–1121, 1953.
141. Roseman, S., and Dorfman, A.: Effect of gentisic acid and related compounds on bovine testicular hyaluronidase, J. Biol. Chem. *199*:345–355, 1952.
142. Roseman, S., and Dorfman, A.: Determination and metabolism of gentisic acid, J. Biol. Chem. *192*:105–114, 1952.
143. Floris, E.: Il potenziamento dell'effetto cortisonico del salicilato di sodio come mezzo per accrescerne l'azione antireumatica, Rassegna med. sarda *56*:369–385, 1954.
144. Eades, C. H., Jr., and King, J. S., Jr.: A strain-dependent influence of glycine on salicylate-induced adrenal ascorbic acid depletion in rats, Federation Proc. *15*:246, 1956.
145. Costa, E., and Ferrari, W.: Über die Fähigkeit des Glykokolls die Nebennierenrinde empfindlicher in Gegenwart der antirheumatischen Stoffe zu machen, Arch. internat. de pharmacodyn. et de thérap. *104*:113–119, 1955.
146. Ronzoni, E., and Reichlin, S.: Adrenergic agents and the adrenocorticotrophic action of the anterior pituitary, Am. J. Physiol. *160*:490–498, 1950.
147. Voot, M.: Control of the secretory activity of the adrenal cortex. *In:* The Adrenal Cortex, Proceedings of the 5th Symposium of the Colston Research Society, London, Butterworth, 1953, pp. 59–68.
148. Oláh, F.; Varró, V.; Majoros, M.; Kovacs, K., and Bachrach, D.: Adrenalin és cortison eosinopeniát okozó hatásának gátlása evipanatruim narkózissal, Orvosi Hetilap *92*:1129, 1951.
149. Harris, G. W., and Fortier, C.: The regulation of anterior pituitary function, with special reference to the secretion of adrenocorticotrophic hormone. *In:* Selye, H., and Heuser, G.: Fourth Annual Report on Stress, Montreal, Acta, Inc., 1954, pp. 106–127.
150. Cauwenberge, H. Van, and Betz, H.: Salicylate and neuro-endocrine stimulation, Lancet *1*:1083–1086, 1952.
151. Kelemen, E.; Tanos, B.; Soltész, R., and Hadju, L.: The mechanism of salicylate shock, Lancet *1*:549, 1953.
152. Cauwenberge, H. Van: Réaction de l'axe hypothalamo-hypophyso-surrénalien a la Dibénamine, a l'adrenaline, et au salicylate de soude, Ann. d'endocrinol. *13*:390–394, 1952.
153. Selye, H., and Horava, A.: Second Annual Report on Stress—1952, Montreal, Acta, Inc., 1952.
154. Selye, H., and Horava, A.: Third Annual Report on Stress—1953, Montreal, Acta, Inc., 1953.
155. Selye, H., and Heuser, G.: Fourth Annual Report on Stress—1954, Montreal, Acta, Inc., 1954.
156. Selye, H., and Heuser, G.: Fifth Annual Report on Stress—1955–56, New York, Medical Encyclopedia, Inc., 1956.

A new, essential, and timely book

ANTIBIOTICS ANNUAL 1955-1956

Edited by Henry Welch, Ph.D., and Félix Martí-Ibáñez, M.D.

Proceedings of the Third Annual Symposium on Antibiotics, Washington, D. C., November 2, 3, and 4, 1955

150 REPORTS ON THE LATEST FINDINGS IN ANTIBIOTICS

by

375 AUTHORS REPRESENTING 16 COUNTRIES

Panel Discussions

- Long-Term and Prophylactic Use of Antibiotics—Harry F. Dowling, Moderator
- Penicillin V—Morton Hamburger, Moderator
- True Significance and Real Incidence of Reactions Following Clinical Use of Antibiotics—Maxwell Finland, Moderator

Some Selected Subjects Among the 150 Papers

- New developments in streptomycin therapy;
- A comparison of various antibiotic agents in pre and postoperative therapy;
- Further reports on the new antibiotic cycloserine;
- Complete descriptions of research on 12 new antibiotics: carbomycin, spiramycin, eulicin, 1968 (an antifungal agent), actidione, thiostrepton, amphotericin, streptolydigin, cathomycin, rubidin, vancomycin, puromycin;
- The value of combined antibiotic-vitamin therapy;
- Newest indications for tetracycline therapy;
- 15 reports on laboratory procedures for antibiotics, including sensitivity and synergistic studies;
- Penicillin V, the new oral form of penicillin: its pharmacology and clinical usefulness;
- Antibiotics in animal husbandry: growth studies, meat preservation, and control of animal infections;
- 7 reports on resistance as a problem in antibiotic therapy, plus re-evaluations of side effects following administration of antibiotics.

ONLY $10.00 per copy for this attractive, hardbound volume of about 1,000 pages in length, including charts and illustrations.

A Unique and Indispensable Volume for Every Physician, Research Worker, and Teacher

To order copies, write the publisher:

MEDICAL ENCYCLOPEDIA, INC., 30 East 60th Street, New York 22, N. Y.

for

pediatric

practice...

TERRAMYCIN®

BRAND OF OXYTETRACYCLINE

"Our clinical observations indicate that a dosage of 3 to 5 mg./lb./day, given in 1 injection daily, is adequate for oxytetracycline (Terramycin)-sensitive infections of moderate severity, and as such, is practical for use in home and office pediatric practice. This is particularly feasible in the younger age group, in whom this dosage can readily be given in 1 injection in a 24 hour period, and in whom this form of therapy may be most often indicated.

Particular reference is directed to ... the low incidence of local reactions."

Schreiber, E. J., Robinson, F. L., and Forney, W. I.: Antibiotic Med. 1:453, Aug. 1955.

... hydrochloride (Terramycin) with 5% magnesium chloride and 2% procaine hydrochloride.

PFIZER LABORATORIES, Division, Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.